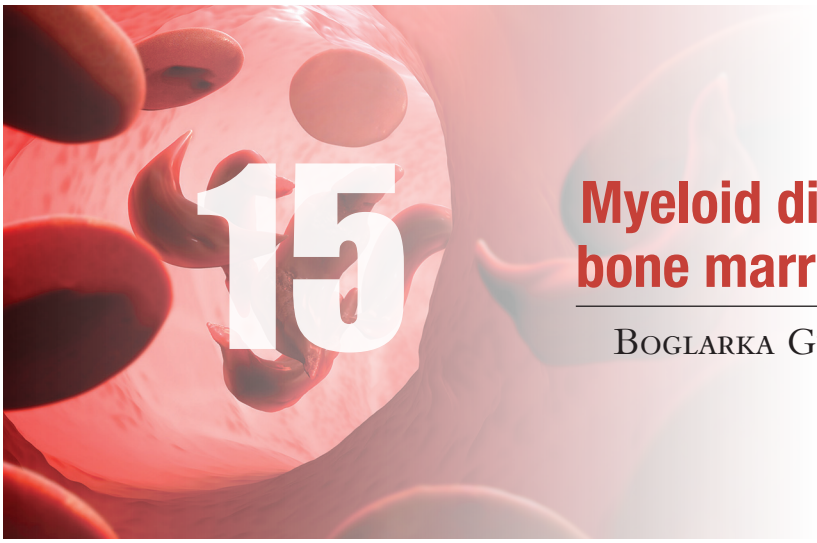

15 Myeloid disorders and inherited bone marrow failure syndromes

Boglarka Gyurkocza, Marcin Wlodarski, and Cynthia E. Dunbar

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Introduction

The term *myeloid* derives from the Greek *myelos*, meaning "marrow," and, in its broadest sense, is used to describe hematologic conditions or diseases originating in the bone marrow (BM). *Myeloid* is also used more narrowly to describe disorders primarily involving granulocytes (neutrophils, eosinophils, or basophils) and monocytes, as opposed to other cell lineages such as lymphoid cells. A variety of myeloid disorders are described in this chapter, including inherited and acquired neutropenias, neutrophilia, neutrophil function abnormalities, acquired and inherited histocytic and autoinflammatory disorders, and macrophage storage disorders.

BM failure refers to the inability of BM hematopoiesis to meet physiologic demands for *production* of healthy blood cells due to dysfunction or loss of hematopoietic stem or progenitor cells (HSPCs). Pancytopenia with reduced red cells, neutrophils and platelets, or bi- or unilineage cytopenias may result. Lymphocyte numbers are usually preserved, due to self-renewal abilities of mature T cells. Initial differential diagnosis of cytopenias first requires distinguishing production defects from peripheral destruction, consumption, or blood loss. Besides BM examination, reduced numbers of reticulocytes and/or immature platelets and/or an elevated mean cell volume may suggest a BM failure syndrome. BM failure syndromes can be classified into acquired idiopathic, inherited, iatrogenic or environmental (ie, radiation or chemotherapy), or those due to vitamin/nutrient deficiency. Acquired

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Off-label drug use: Androgens (oxymetholone or danazol) in Fanconi anemia and telomeropathies; G-CSF in non-SCN neutropenia; glucocorticoids in Diamond-Blackfan anemia, autoimmune neutropenias, and histiocytic syndromes; iron chelating agents in congenital dyserythropoietic anemias; interferon-γ in congenital dyserythropoietic anemia type I and Erdheim-Chester disease; plerixafor in WHIM syndrome; intravenous immunoglobin in autoimmune neutropenias; interferon-γ in chronic granulomatous disease; colchicine in familial Mediterranean fever; etoposide, methotrexate, cyclosporine, antithymocyte globulin, and dexamethasone in hemophagocytic lymphohistiocytosis; topical steroids, nitrogen mustard, psoralen in Langerhans cell histiocytosis; vinblastine, methotrexate, and glucocorticoids in Langerhans cell histiocytosis.

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BM failure states, including aplastic anemia (AA) and myelodysplasia (MDS), are discussed in Chapter 18.

The range of molecular mechanisms responsible for inherited BM failure states (discussed in this chapter) is broad, including abnormal DNA damage response (Fanconi anemia [FA]), defective ribosome biogenesis (Diamond-Blackfan anemia [DBA] and Shwachman-Diamond syndrome [SDS]), defective telomere maintenance (dyskeratosis congenita [DC] and other telomere biology disorders [TBDs] termed "telomeropathies"), abnormalities of central hematologic transcription factors (GATA2 deficiency) or growth suppression genes (SAMD9/SAMD9L syndromes), and altered hematopoietic growth factor receptor–kinase signaling (congenital amegakaryocytic thrombocytopenia [CAMT]). Many but not all inherited BM failure syndromes (IBMFS) convey an increased risk of eventual progression to MDS or leukemia, whether due to chronic proliferative stress acting on remaining HSPCs or an increase in genotoxic events. In this chapter, we also include discussion of myeloid leukemia predisposition syndromes often presenting with clinically significant bone marrow failure prior to neoplastic transformation. We focus on those marrow failure states presenting primarily with hematologic manifestations and thus cared for by hematologists, omitting some rare fatal genetic disorders presenting in infancy or childhood with severe neurologic and/or multisystem failure along with cytopenias

Granulocytes: neutrophils, eosinophils, and basophils

The term *granulocytes* encompasses circulating neutrophils, eosinophils, and basophils, although, because of vast neutrophil predominance in the blood compared to other granulocytes, the terms *neutrophil* and *granulocyte* are sometimes used synonymously. Neutrophils are a critical component of the innate immune response, and persistent neutropenia is associated with a marked susceptibility to bacterial and fungal infections. Conversely, neutrophils are also a major contributor to tissue damage in inflammatory diseases. Neutrophil homeostasis in the blood is regulated at 3 levels: neutrophil production in the BM, neutrophil release from the BM to blood, and neutrophil clearance from the blood (Figure 15-1).

Neutrophils

Neutrophil production

Under normal conditions, neutrophils are produced exclusively in the BM, where it is estimated that 10^{12} are generated on a daily basis. Neutrophilic differentiation from multipotent HSPC is regulated by the coordinated expression of a number of key myeloid transcription factors, including CCAAT enhancer–binding proteins α (C/EBPα), C/EBPε, and GFI-1. A number of hematopoietic growth factors provide extrinsic signals that regulate various stages along HSPC differentiation toward myeloid lineages, including neutrophils. G-CSF stimulates the proliferation of precursors, reduces the average transit time through the precursor compartment, mediates neutrophil release from the BM, and prevents apoptosis of mature cells.

Neutrophil release

Neutrophils are released from the BM into the blood in a regulated fashion to maintain homeostatic levels of circulating neutrophils. The BM provides a large reservoir of mature neutrophils that can be mobilized readily in response to infection or inflammation. A broad range of substances have been shown to induce neutrophil release from the BM, including chemokines, cytokines, microbial products, and various other inflammatory mediators. The chemokine CXCL12 (originally termed stromal derived factor-1) and the cognate chemokine receptor CXCR4 play a key role in retaining a pool of neutrophils in the BM, whereas the chemokine receptor CXCR2 and its ligands play a role in their release.

Neutrophil clearance

Neutrophil homeostasis in the blood is determined, in part, by the rate of clearance from the circulation. Once released into the circulation, neutrophils have been thought to have a short half-life of only 5 to 6 hours; however, the most recent studies suggest some neutrophils may persist in the circulation for up to 5 to 6 days. Neutrophils are cleared primarily in the liver, spleen, or BM, where apoptotic or aged neutrophils are phagocytosed by macrophages.

Neutrophil margination and tissue extravasation

Neutrophils in the circulation loosely attach and subsequently adhere to vascular endothelium in response to the local production of inflammatory cytokines and chemokines, a process termed margination (Figure 15-1). Normally, approximately one-half of the neutrophils in the circulation are in this marginal pool. Selectins mediate neutrophil rolling along the endothelium, and β_2-integrins mediate firm adherence and vascular transmigration. Indeed, deficiency of selectin ligands or β_2-integrins causes leukocyte adhesion deficiency (LAD) (see the following).

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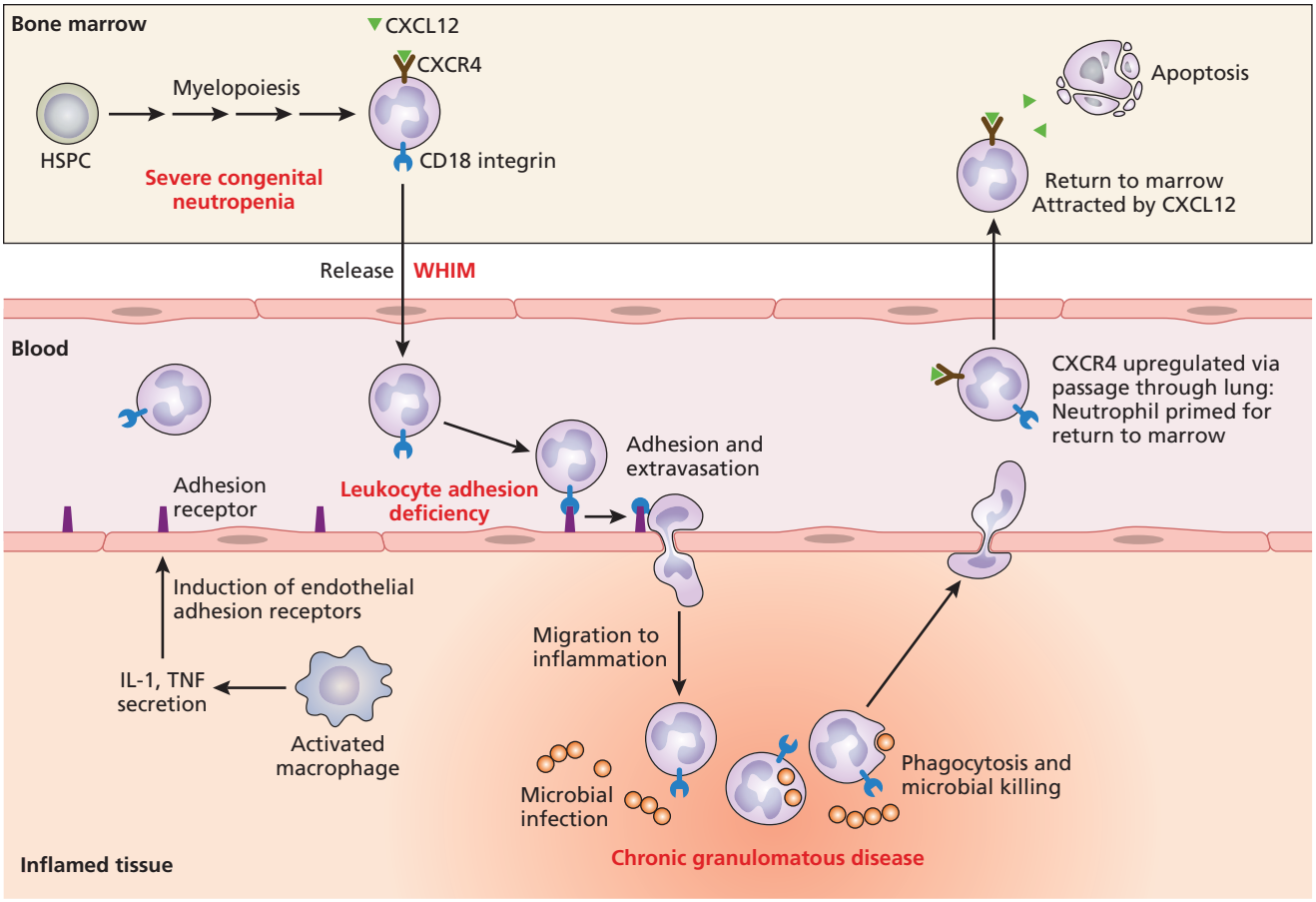

Figure 15-1 The neutrophil life cycle and inherited myeloid disorders. Red text indicates congenital disorders linked to defects in various stages in the neutrophil life cycle. The BM is the primary site of myeloid development in humans. In SCN, neutrophil development in the marrow is blocked prior to completion. Under basal conditions, the BM retains a large reservoir of mature neutrophils, mediated primarily via CXCL12 ligand/CXCR4 receptor interactions. In WHIM syndrome, a hyperactive CXCR4 receptor on neutrophils results in an increase in neutrophil retention in the marrow (myelokathexis). In response to tissue inflammation, circulating neutrophils adhere to endothelium via CD18 integrin binding to adhesion molecules on endothelial cells induced by inflammatory mediators such as IL-1. Via diapedesis, neutrophils then move through the endothelium and migrate along chemokine gradients to reach the site of inflammation. In LAD type 1, lack of functional CD18 results in lack of adhesion and defective tissue entry. Once neutrophils reach the site of inflammation, phagocytosis of bacteria and fungi occurs. In CGD, mutations in components of the NADPH oxidase complex result in impaired microbial killing. Neutrophils return to the circulation from tissues, upregulate CXCR4 following transit through the lung, and home back to the BM in response to a CXCL12 gradient, resulting in apoptosis and clearance of senescent neutrophils.

Once recruited to an infected tissue site, neutrophils serve phagocytic, immunomodulatory, and remodeling functions. They express cell surface receptors binding both immunoglobulins and complement, thus facilitating ingestion and killing of microorganisms. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzymes, localized in neutrophil primary and secondary granules, are involved in the intracellular oxidative burst that accompanies phagocytosis and destruction of microorganisms. These pathways are critical for normal host defense, and mutations in these enzymes can result in diseases characterized by enhanced susceptibility to infection, such as chronic granulomatous disease (CGD) (see the following). Neutrophils also infiltrate tumors and have been associated with both antitumor and protumor effects. Until recently, neutrophil egress from the circulation was considered to be one-way, but imaging and tracking studies now document return of neutrophils back to the circulation from tissues, before final trafficking back to the BM and terminal apoptosis.

Neutrophilia

Neutrophilia is an excess of circulating neutrophils and is typically defined as an *absolute neutrophil count* (ANC) >2 standard deviations above the mean. Neutrophilia is associated with a wide variety of normal physiologic

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conditions, response to stress, and benign and neoplastic disorders (Table 15-1). A prompt increase in the blood neutrophil count, as well as the circulating levels of other leukocytes, occurs with exercise, stress responses including release of ephinephrine/norepinephrine, and some drugs—most notably corticosteroids or beta-adrenergic agonists. Only rarely does this response more than double the ANC. These factors are thought to rapidly increase the numbers of circulating neutrophils due to demargination of cells from vessel walls, not to release of new neutrophils from the marrow.

Neutrophilia associated with infections and inflammatory disorders occurs by 2 general mechanisms. First, during infection, a number of inflammatory cytokines are released into the circulation that induces the release of mature neutrophils from the BM. Second, the sustained cytokine and inflammatory response associated with infections stimulates neutrophil production in the BM. In contrast to neutrophil demargination, neutrophilia associated with infections and inflammatory disorders is marked by an increase in the number of immature neutrophils in the blood, including band forms, metamyelocytes, and even earlier precursors. In addition, neutrophil morphology can change, with appearance of vacuoles and more intensely staining "toxic granulations." Cells released prematurely also may contain bits of endoplasmic reticulum that stain as blue bodies in the cytoplasm, called Döhle bodies (Figure 15-2).

In most cases of reactive neutrophilia, the inciting infection (or other stress) is usually clinically obvious, and neutrophilia is self-limited. In patients with persistent neutrophilia but without demonstration of a clonal marker by either cytogenetic or molecular testing, clinical features such as the presence of splenomegaly, leukoerythroblastic features on the blood smear (presence of teardrop and nucleated red blood cells (RBCs) and immature myeloid cells), basophilia, or circulating promyelocytes or blasts are highly suggestive of an underlying myeloproliferative disorder (MPD) or MPD/MDS (see Chapter 17). In some cases, chronic neutrophilia may result from inherited intrinsic defects of neutrophil function, trafficking, or inflammatory syndromes, as presented in detail later in this chapter.

Table 15-1 Causes of neutrophilia

Acute neutrophilia	Chronic neutrophilia
Acute infections Many localized and systemic acute bacterial, mycotic, rickettsial, spirochetal, and certain viral infections	**Chronic infections** Fungal and mycobacterial infections
Inflammation or tissue necrosis Burns, electric shock, trauma, myocardial infarction, gout, vasculitis, antigen-antibody complexes, complement activation	**Inflammation** Continuation of most acute inflammatory reactions, such as rheumatoid arthritis, gout, chronic vasculitis, myositis, nephritis, colitis, pancreatitis, dermatitis, thyroiditis, drug-sensitivity reactions, periodontitis, Sweet syndrome, familial periodic fever syndromes
Physical or emotional stimuli Cold, heat, exercise, convulsions, pain, labor, anesthesia, surgery, severe stress	**Tumors** Any tumors, but especially gastric, lung, breast, renal, hepatic, pancreatic, uterine, and squamous cell cancers
Drugs, hormones, and toxins Epinephrine, etiocholanolone, endotoxin, glucocorticoids, venoms, vaccines, colony-stimulating factors, rebound from drug-induced agranulocytosis, repletion therapy of megaloblastic anemias	**Drugs, hormones, and toxins** Cigarette smoking, continued exposure to many substances that produce acute neutrophilia; lithium; rarely, as a reaction to other drugs
	Metabolic and endocrinologic disorders Pregnancy and lactation, eclampsia, thyroid storm, Cushing disease
	Hematologic disorders Chronic hemolysis or hemorrhage, asplenia, myeloproliferative disorders, overlap myelodysplastic/myeloproliferative disorders
	Hereditary and congenital disorders Down syndrome, familial Mediterranean fever, leukocyte adhesion deficiency, hereditary neutrophilia
	Chronic idiopathic neutrophilia

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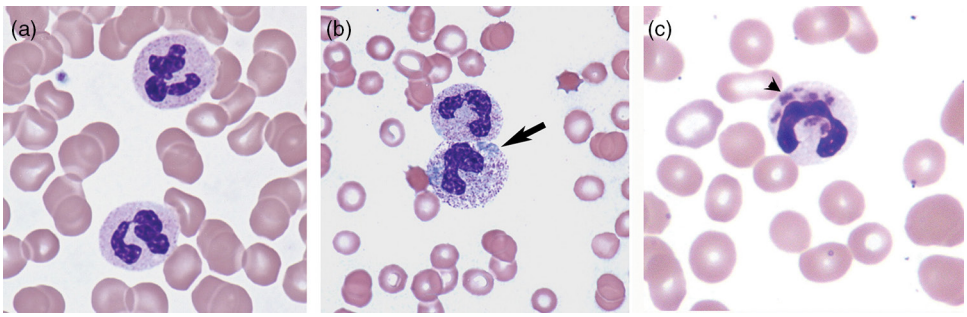

Figure 15-2 Normal and abnormal neutrophil morphology. Photomicrographs of blood smears showing typical neutrophil morphology from a healthy individual (A), a patient with sepsis showing Döhle bodies (arrow) and toxic granulations (B), and a patient with Chédiak-Higashi syndrome showing large cytoplasmic inclusions (arrowhead) (C). Source: ASH Image Bank, images 3780 (A), 3778 (B), and 2979 (C).

Neutropenia

Neutropenia is commonly defined as an ANC of <1500 cells/μL; however, neutrophil levels can be lower (generally 500-1500 cells/μL) throughout life in some healthy individuals without an increase in susceptibility to infections. Because the incidence of this laboratory finding was first noted to be higher in individuals from some ethnic and racial groups (eg, Africans, African-Americans, Caribbean-Americans and Yemenite Jews) as compared to those of European descent, it was initially termed benign ethnic neutropenia. However, more recent studies have demonstrated that this range of neutrophil levels without infectious complications can be found in individuals from any racial or ethnic group, and the term benign constitutional neutropenia (BCN) is more accurate and is now preferred.

Homozygosity for a single nucleotide polymorphism (SNP) in the *ACKR1* gene, encoding the minor blood group antigen Duffy antigen receptor for chemokines (DARC), has been linked to BCN as well as to Duffy negative red blood cells. This SNP is partially protective against malarial infection, potentially explaining its increased frequency in human populations evolving in malarial zones, however, the same SNP is linked to BCN in all populations. Systems controlling steady-state neutrophil numbers are poorly understood, and work continues to decipher why a Duffy negative phenotype results in neutropenia. Evidence to date suggests a relative shift in neutrophil distribution to tissues from the blood.

Neutropenia is classified based on the ANC as severe (<500/μL), moderate (500 to 1000/μL), or mild (1000 to 1500/μL). The risk of infection increases when the ANC falls below 500/μL; however, risk of the most serious infections rises sharply with ANC <200/μL. Patients with neutropenia are prone to develop bacterial infections, typically caused by endogenous flora and involving mucous membranes, including gingivitis, stomatitis, perirectal abscesses, cellulitis, and pneumonia. Fungal infections are a major cause of mortality in patients with chronic severe neutropenia. There is no increase in susceptibility to viral or parasitic infections with isolated neutropenia. It is important to take into account whether neutrophil counts are falling or recovering and whether neutrophil function itself may also be impaired (eg, in MDS) when assessing the clinical risk of neutropenia. For example, a falling neutrophil count of 600/μL in a patient following chemotherapy is more worrisome than a stable count of 600/μL in an individual with lupus or another autoimmune disease.

The differential diagnosis of neutropenia is broad (Table 15-2). In addition to inherited neutropenias to be discussed in this chapter, neutropenia is a frequent manifestation of MDS, acute leukemias, autoimmune disorders, and marrow-infiltrative processes such as myelofibrosis, or metastatic carcinoma; these are discussed in detail in their respective chapters.

Eosinophils and basophils

Marrow HPSC produce a small proportion of eosinophils and basophils. The granules of eosinophils contain histamine and proteins important for the killing of parasites. Normal blood eosinophil counts range from 0.05-0.5X 10^9/L, however, most eosinophils are located in tissues, particularly the gastrointestinal tract, spleen, and lymph nodes. Eosinophil production and/or lifespan is increased, with higher circulating eosinophil counts, in allergic disorders (eg, asthma, allergic rhinitis, dermatitis), parasitic infections, collagen vascular diseases, and drug reactions.

Clinically relevant hypereosinophilic syndromes of any etiology are defined by a persistent eosinophil count of >1.5 × 10^9/L or marked tissue eosinophil infiltration and clinical manifestations attributable to hypereosinophilia. Tissue

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Table 15-2 Causes of neutropenia

Inherited neutropenia syndromes*
Severe congenital neutropenia (sometimes termed Kostmann syndrome)
Cyclic neutropenia
Shwachman-Diamond syndrome
WHIM syndrome (myelokathexis)
Chédiak-Higashi syndrome and other disorders of vesicular transport
Pearson syndrome (+/− anemia)
GATA2 deficiency (isolated neutropenia rare)
Fanconi anemia (isolated neutropenia rare)
Dyskeratosis congenita/telomere biology disorders (isolated neutropenia rare)
Acquired neutropenia
Neonatal alloimmune neutropenia
Primary autoimmune neutropenia
Secondary autoimmune neutropenias, eg, lupus erythematosus, rheumatoid arthritis (Felty syndrome), etc
Nutritional deficiencies (vitamin B_{12}, folic acid, copper)
Myelodysplastic syndromes
Acute leukemias and other hematologic malignancies
Myelophthisis (BM infiltration by tumor, fibrosis, granulomas)
Large granular lymphocytic leukemia
Neutropenia associated with viral, fungal, or bacterial infections or sepsis
Drug-induced neutropenia
Hypersplenism

*Not restricted to disorders in which neutropenia is the only manifestation.

damage results both from direct damage due to release of granule contents and from stimulation of other effector cells via release of inflammatory mediators. Paraneoplastic eosinophilia can result from malignant lymphoid cells releasing of interleukin-5 (IL-5), the primary cytokine supporting eosinophil production and survival. The pathophysiology of myeloproliferative clonal hypereosinophilic syndromes are discussed in Chapter 17. Treatment is initiated based on end-organ damage (particularly to heart and lungs) and symptoms, and corticosteroids are often an effective initial intervention. Additional treatment depends whether the underlying extrinsic cause can be reversed (ie, lymphoma or parasitemia) or the clonal neoplasm can be treated with a tyrosine kinase inhibitor (see Chapter 17).

Basophils are the least numerous blood leukocytes. Basophilic granules contain histamine, glycosaminoglycans, major basic protein, proteases, and a variety of other vasoactive inflammatory mediators. Basophils primarily function to activate immediate (type 1) hypersensitivity responses. Basophilia is associated with hypersensitivity reactions, including drug and food allergies. Basophilia is a common feature of MPDs, particularly chronic myeloid leukemia, and can aid in diagnosis of these disorders. Basophilia also can be associated with other chronic inflammatory diseases, such as tuberculosis, ulcerative colitis, and rheumatoid arthritis (RA), but is rarely seen as an isolated finding.

Monocytes and related cells

Monocytes and related histocytes and macrophages serve antimicrobial, scavenger, and secretory functions and also participate in tissue repair and antigen processing and presentation. Monocytes serve as precursors for both circulating macrophages and tissue-associated cells related to macrophages. These cells are often associated with the endothelium, particularly in the spleen and liver, where they clear microorganisms and aged or damaged blood cells from the circulation. Alveolar macrophages in the lung, Kupffer cells in the liver, sinus histocytes in lymph nodes, Langerhans cells in the skin, microglia in the central nervous system (CNS), and osteoclasts in the bone are all forms of tissue histiocytes or macrophages that are thought to derive from blood monocytes. These tissue populations may be very long-lived, populated originally from monocytes or monocyte precursors migrating to tissues during fetal development, followed by heterogeneous replacement via blood monocytes in various tissues postnatally.

Monocytes and related cells are a primary source of the inflammatory cytokines (eg, tumor necrosis factor, interleukin-1, interferons) that cause fever and many of the symptoms associated with infections or inflammation. Tissue macrophages can serve both proinflammatory and anti-inflammatory functions via production of various cytokines. Chronic or dysregulated stimulation of tissue macrophages may contribute to acquired or inherited systemic inflammatory syndromes, and anti-inflammatory macrophages may play a central role in the ability of tumors to evade the immune system.

Dendritic cells share a precursor with monocytes and consist of several subtypes of cells that participate in both innate and adaptive immune responses. These cells are distributed widely throughout virtually all tissues, particularly concentrated in lymphoid tissues associated with barriers, such as the skin and mucosal surfaces. A major function of dendritic cells is to process and present antigens to T cells. Immature dendritic cells in the peripheral tissue express surface receptors that allow them to recognize and take up extracellular antigens in their environment, stimulating activation, maturation, and migration to secondary lymphoid tissues, where they bind and present antigen in the

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context of major histocompatibility complex class I and II molecules to stimulate naive T cells. The ability of dendritic cells to present tumor antigens has led to their use in vaccine immunotherapy trials.

Monocytosis

Monocytes normally account for approximately 1% to 9% of peripheral blood leukocytes, with absolute monocyte counts ranging from 0.3×10^9 to 0.7×10^9/L. An increase in circulating monocytes may be observed in chronic inflammatory conditions and chronic infections, such as tuberculosis, endocarditis, and syphilis. In inflammatory conditions, monocytosis is a reactive process resulting from the peripheral production of cytokines, which stimulate monocyte production. Monocytosis is a hallmark of the MPD/MDS overlap syndrome chronic myelomonocytic leukemia and of the pediatric disorder juvenile myelomonocytic leukemia. It may also be observed in association with lymphomas and acute monocytic (monoblastic) leukemias. Malignant monocytosis is presumed to be due to specific molecular defects affecting monocyte proliferation, differentiation, and survival.

Monocytopenia

Transient monocytopenia occurs with stress and various infections including overwhelming sepsis and as a result of cytotoxic chemotherapy. A decreased absolute monocyte count can be encountered in acquired BM failure states such as aplastic anemia and, less commonly, MDS. Monocyte numbers and function are maintained in many other conditions that cause neutropenia. Monocytopenia in association with natural killer (NK) cell deficiency and B-cell lymphopenia can be part of the spectrum of GATA2 deficiency. Monocytopenia, along with neutropenia, is also characteristic of hairy cell leukemia.

Inherited neutropenias

Severe congenital neutropenia and cyclic neutropenia

CLINICAL CASE

A 4-month-old male infant presented with inflamed gums and severe bacterial pneumonia and was found to have an ANC of 20/μL, a normal platelet count, and normal red cell parameters. The infant had no developmental abnormalities. The pneumonia was treated with antibiotics, and weekly blood counts showed no change in the neutrophil count. Treatment with G-CSF raised the neutrophil count to >1000/μL.

Definition and clinical features

Severe congenital neutropenia (SCN), often termed Kostmann syndrome, presents in infancy with fever and severe infections, resulting in early death in the absence of treatment directed at increasing the neutrophil count. The ANC is often $<0.2 \times 10^9$/L, with normal red blood cell and platelet counts. The BM shows maturation arrest of myelopoiesis, with abundant promyelocytes but a marked reduction in myelocytes, metamyelocytes, and neutrophils.

Congenital cyclic neutropenia (CyN) is characterized by regular cycles of severe neutropenia reaching a nadir most commonly (but not universally) every 21 days. At the nadir, patients may develop fever and mouth ulcers and, at times, serious infections. Differential diagnosis of SCN and CyN include benign constitutional neutropenia, infections, and other inherited BM failure syndromes.

Patients with SCN are at risk for progression to acute myelogenous leukemia (AML), particularly with acquisition of *RUNX1* somatic mutations. As detailed in the following, SCN patients on chronic G-CSF treatment frequently acquire somatic activating *CSF3R* mutations.

Pathophysiology

CyN families were initially identified as having autosomal dominant disease mutations in the *ELANE* gene-encoding neutrophil elastase (NE). A surprising twist was the subsequent identification of *ELANE* mutations in many patients with SCN. NE is a serine protease that is synthesized predominantly in promyelocytes. *ELANE* mutations appear to result in accumulation of a misfolded protein or mistrafficking of the mutant protein, which is hypothesized to trigger apoptosis in myeloid progenitors via an unfolded protein response or dyfunctional proteolysis. Why certain mutations result in CyN versus SCN is unclear. Another puzzling observation is that *ELANE*-mutated SCN patients have high risk for development of AML, while the risk appears much lower in CyN, with only a few AML cases recently reported.

In contrast to the more common autosomal dominant *ELANE*–mutated SCN, the original family described by Kostmann had autosomal recessive SCN, subsequently linked to biallelic mutations in the *HAX1* gene, found to account for ~10% of SCN. The HAX1 protein is a regulator of mitochondrial membrane potential and apoptosis, although it is unclear why premature death of neutrophils is specifically associated with HAX1 deficiency. Additional causes of SCN include biallelic mutations in *G6PC3* or activating mutations in the X chromosome Wiscott-Aldrich syndrome (WAS) gene (in contrast to loss-of-function mutations in classic WAS resulting in thrombocytopenia and immunodeficiency). Additional

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mutated genes linked to the phenotype of congenital neutropenia include *JAGN1, GFI1, VPS45A*, and *TCRG1,* but this list is not exhaustive.

Treatment

The availability of G-CSF has revolutionized the outcomes of patients with SCN and CyN. Chronic G-CSF treatment increases the neutrophil count in SCN, resulting in decreased frequency of infections and increased survival. With longer survival, a 20% to 25% risk of progression to AML has been appreciated. Common acquired somatic mutations in SCN occur in the gene that encodes the G-CSF receptor (*CSF3R*), deleting an inhibitory cytoplasmic domain of the receptor, rendering clones hypersensitive to G-CSF. While the mutations increase the risk of progression to AML, the time course is variable, and clonal dominance can decrease with G-CSF discontinuation or dose reduction. *RUNX1* mutations have been frequently documented in SCN patients prior to leukemic progression. Leukemic transformation occurred in patients with congenital neutropenia prior to the availability of G-CSF, and the precise contribution of G-CSF therapy to the development of *CSF3R* gene mutations in SCN remains unclear. For SCN patients who become refractory to G-CSF or who develop leukemia, hematopoietic cell transplantation (HSCT) may be appropriate and curative.

G-CSF therapy of CyN reduces the duration of neutropenic nadirs and severe infections. As noted previously, progression to AML in CyN is very rare, even with prolonged G-CSF therapy.

KEY POINTS

- SCN presents in infancy with profound neutropenia and can be treated effectively with G-CSF.
- CyN is characterized by approximately 21-day cycles of neutropenia and can be treated effectively by G-CSF.
- Both SCN and CyN are associated with mutations in the neutrophil elastase (*ELANE*) gene, resulting in premature death of developing myeloid cells.
- SCN and to a much lesser degree CyN patients have an increased risk of AML, associated with acquired somatic mutations in the G-CSF receptor (*CSF3R*) or *RUNX1* genes.

WHIM syndrome

WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) syndrome is a rare autosomal dominant disorder characterized by neutropenia, B-cell lymphopenia, hypogammaglobulinemia, and human papillomavirus (HPV)-associated warts and carcinomas. Affected individuals typically present with recurrent bacterial infections in the setting of moderate neutropenia. Despite the peripheral neutropenia, the BM of affected patients is hypercellular with retention of *increased* numbers of mature neutrophils (a finding termed *myelokathexis*).

The majority of patients with WHIM syndrome have heterozygous mutations of the *CXCR4* gene. CXCR4 is a G protein-coupled receptor for SDF1 (CXCL12), and SDF1/CXCR4 signaling results in neutrophil retention within the BM. The mutations of *CXCR4* in WHIM syndrome result in *enhanced* CXCR4 signaling, increasing BM neutrophil retention and causing peripheral neutropenia and likely also result in abnormal B-cell trafficking and, thus, function.

G-CSF is effective in increasing circulating neutrophil numbers but does not impact on the B-cell abnormalities and infection risk in WHIM patients. Those with significant hypogammaglobulinemia may benefit from intravenous immunoglobulin (IVIG) therapy. Surveillance and surgical removal of dysplastic skin or mucosal HPV-related lesions is important. Given that many of the clinical features affecting patients with WHIM are a consequence of hyperfunction of CXCR4, an inhibitor of CXCR4 (plerixafor) has been shown to be effective reversing cytopenias, myelokathexis, and HPV-related disease.

KEY POINTS

- WHIM syndrome is characterized by HPV-related lesions, hypogammaglobulinemia with recurrent infections, and BM myelokathexis resulting in neutropenia.
- WHIM syndrome is caused by autosomal dominant heterozygous mutations in the *CXCR4* gene, resulting in overactivity of CXCR4/CXCL12 signaling and retention of neutrophils in the BM.
- Clinical management includes IVIG, prophylactic antibiotics, and plerixafor.

Acquired neutropenias

Primary autoimmune neutropenia

Primary autoimmune neutropenia most typically occurs in children but can occur anytime up through adulthood in patients without other autoimmune disorders. The ANC is typically between 500 and 1000/μL. Serious infections are infrequent and may reflect the ability of patients to increase their neutrophil counts in response to stress. BM examination is rarely indicated. When performed, it reveals

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minimal abnormalities or a deficit of mature neutrophils only. Spontaneous remission occurs in most patients, usually within 24 months of diagnosis. The pathogenesis is thought to be immune-mediated neutrophil clearance. Indeed, in the great majority of published cases, antibodies to neutrophil antigens such as FCγRIII or CDllb/CD18 can be detected. Many patients remain free of infections, and no specific therapy is required. Hence, they represent a subset of patients diagnosed with chronic benign neutropenia. For patients with recurrent infections, prophylactic antibiotics or intermittent treatment with G-CSF may be indicated. Although rarely needed, high-dose IVIg or corticosteroid therapy has been reported to be effective.

Secondary autoimmune neutropenia

Neutropenia occasionally is associated with autoimmune disease, most commonly rheumatoid arthritis, systemic lupus erythematosus (SLE), or Sjögren syndrome. Moreover, there is a strong association of neutropenia with large granular lymphocytic leukemia (LGL), often in association with RA. In SLE, neutropenia occurs in ~50% of patients. The neutropenia is generally mild, has little impact on prognosis, and requires no specific treatment. The pathogenesis of neutropenia in SLE is thought result from accelerated apoptosis of mature neutrophils. Although neutrophil antibodies have been implicated, the clinical utility of measuring antineutrophil antibodies in SLE is questionable. The differential diagnosis for neutropenia in RA is wide, and drug-induced neutropenia must be considered. Felty syndrome is the triad of unexplained often profound neutropenia, RA, and splenomegaly. Unlike the neutropenia associated with other autoimmune diseases, there is an increased risk of infections in patients with Felty syndrome. Treatment is most commonly directed at the underlying autoimmune disease.

Chronic idiopathic neutropenia

In a subset of patients with acquired chronic neutropenia, most commonly young-middle aged women, there is no clear evidence of immune-mediated disease, although a T cell–mediated etiology cannot be ruled out. The diagnosis of chronic idiopathic neutropenia is based on the presence of persistent acquired neutropenia in the absence of underlying autoimmune disease, cytogenetic abnormalities or dysplasia, antineutrophil antibodies, or other likely explanations for neutropenia. In addition to neutropenia, lymphopenia, monocytopenia, anemia, and thrombocytopenia are occasionally seen. It has been suggested that chronic low-grade inflammation may contribute to neutropenia in some patients. The clinical course is generally benign, infections are infrequent, and specific treatment is not required.

Drug-induced neutropenia

CLINICAL CASE

A 50-year-old teacher with a history of ulcerative colitis presents to the emergency room with fever, chills, and sore throat for 24 hours. On examination, the temperature is 39.6 °C, blood pressure 90/60, pulse 105, and respiratory rate 28. The patient is confused and reports that her throat is very sore. The abdomen is slightly tender, and bowel sounds are absent. Therapeutic measures for septic shock are initiated. A complete blood count reveals a white blood cell count of 1.5×10^9/L with an ANC of 0. On questioning the patient's husband, you learn that she had been in her usual state of health until a few days ago. She has had long-standing complaints of chronic diarrhea with intermittent blood and mucus in the stool. Her only medication is sulfasalazine begun 2 months ago.

Clinical features and epidemiology

Non-chemotherapy drug–induced severe neutropenia or agranulocytosis (complete absence of neutrophils in the blood) are serious medical problems, with an estimated incidence of 2 to 15.4 cases per million and a case fatality rate of approximately 5%. Risk increases with age. Although certain medications carry a higher risk of neutropenia (Table 15-3), it is wise to consider almost any medication as a potential offender, thus emphasizing the need for a careful drug history in all patients who present with acquired neutropenia. A systematic review of the literature in 2007 identified 10 drugs that accounted for ~50% of cases of definite or probable reports of drug-induced agranulocytosis: carbimazole, clozapine, dapsone, dipyrone, methimazole, penicillin G, procainamide, propylthiouracil, rituximab, sulfasalazine, and ticlopidine. Prolonged use of vancomycin is also associated with neutropenia. Serial blood counts are now recommended for patients on some drugs (eg, sulfasalazine and clozapine) because of the relatively high frequency of drug-induced neutropenia associated with these agents. Agranulocytosis has been associated with both cocaine and heroin use, mostly likely due to adulteration with levamisole, a veterinary drug known to be associated with agranulocytosis.

In most cases, agranulocytosis presents within 3 months after starting the offending drug. Patients often have fever and pharyngitis as their first symptoms. Sepsis or pneumonia may occur in 10% to 30% of patients. The disease mechanism is often unclear, although immune-mediated destruction is likely. In some well-studied cases, the offending drug serves as a hapten in association with an endogenous protein, probably an antigen expressed on the

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Table 15-3 Selected drugs associated with neutropenia

Anti-inflammatory agents	Antimicrobial agents
Aminopyrine★	Ampicillin★
Diclofenac★	Cefotazime★
Diflunisal★	Cefuroxime★
Dipyrone★	Flucytosine★
Ibuprofen★	Fusidic acid★
Gold salts	Imipenem-cilastatin★
Penicillamine	Nafcillin★
Phenylbutazone	Oxacillin★
Sulfasalazine	Quinine★
Cardiovascular agents	Ticarcillin★
Clopidogrel★	Chloramphenicol
Disopyramide★	Sulfonamides
Methyldopa★	Amodiaquine
Procainamide★	Dapsone
Quinidine★	Terbinafine
Spironolactone★	Vancomycin
Dipyridamole	**Antithyroid agents**
Captopril	Propylthiouracil★
Ticlopidine	Carbimazole
Anticonvulsants	Methimazole
Phenytoin★	**Other agents**
Carbamazepine	Amygdalin★
Psychotropic agents	Calcium dobesilate★
Chlorpromazine★	Infliximab★
Clozapine★	Levamisole★
Fluoxetine★	Metoclopramide★
Mianserin	Mebhydrolin★
Hypoglycemic agents	Rituximab
Chlorpropamide	Ranitidine
Tolbutamide	Famotidine
Glyburide★	Metiamide

★Level I evidence based on Andersohn F et al, *Ann Intern Med*. 2007;146:657-665.

neutrophil surface then targeted by the immune system. Other drugs may impair production of neutrophils by a direct toxic effect on myeloid precursors. BM examination usually is not necessary in cases with otherwise-normal hemoglobin level, platelet count, and red blood cell morphology.

Management

Management includes prompt withdrawal of all potentially offending drugs and administration of broad-spectrum antibiotics, often with inpatient monitoring awaiting neutrophil recovery. The prognosis is generally good if the offending medication is stopped, because neutrophil counts recover on average within approximately 1 week of discontinuation, although timing can be variable. The time to hematologic recovery may be proportional to the severity of the marrow defect; that is, if no cells at the myelocyte stage are seen on an aspirate sample, it probably will be longer before recovery occurs.

Therapy with hematopoietic growth factors, particularly G-CSF, is controversial. A number of nonrandomized trials have reported a shortened duration of neutropenia, less antibiotic use, and reduced hospital stay with the use of G-CSF. However, the only published prospective, randomized trial, which included just 24 patients, did not demonstrate a benefit of G-CSF administration in this setting. Pending further clinical trials, given that a neutrophil count less than 0.1×10^9/L and the presence of sepsis or severe infection are associated with delayed neutrophil recovery and increased mortality, G-CSF at a dose of 5 μg/day is often recommended for patients with very severe neutropenia.

KEY POINTS

- Autoimmune neutropenias can be isolated or associated with other autoimmune diseases, and if severe are treated with various forms of immunosuppression, G-CSF, and/or antibiotics.
- Neutropenia in adults is frequently due to drugs, both as a predictable response to myelotoxic agents and as an idiosyncratic reaction to almost any drug.
- Treatment of drug-induced neutropenia focuses on stopping the likely causative drug, with recovery beginning by 1 week later.

Inherited disorders of neutrophil function

CLINICAL CASE

A 2-year-old boy with consanguineous parents has had recurrent furuncles and deep abscesses since the birth. On examination, there is no active infection, but there are scars from drainage of previous abscesses. Complete blood count shows a hematocrit of 32%, WBC is 12×10^9/L, and the platelet count is 400×10^9/L. The differential count is normal, and the morphology of the leukocytes is normal. The IgG level is increased; the levels of IgM and IgA are normal. The patient's neutrophils lacked CD18 expression by flow cytometry and he was diagnosed with leukocyte adhesion deficiency type 1.

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Because recurrent fevers, otitis media, and sinopulmonary infections are common in young children, it may be difficult to assess when a child has had "too many" infections despite a normal or elevated neutrophil count. Certain circumstances, however, should raise concern for an underlying neutrophil function disorder and may merit further evaluation. These include the following: (1) severe or unusual bacterial infections (eg, sepsis, osteomyelitis, meningitis, hepatic or brain abscess); (2) recurrent bacterial infections (eg, pneumonia, sinusitis, severe or recurrent staph aureus cellulitis, lymphadenitis, draining otitis media); (4) infections caused by unusual pathogens (eg, *Aspergillus* pneumonia, disseminated candidiasis, *Serratia marcescens*, *Nocardia* species, *Burkholderia cepacia*); and (5) chronic gingivitis or recurrent aphthous ulcers. In the previous clinical case, the history of recurrent abscesses in the setting of a normal ANC would merit further evaluation for a neutrophil function disorder. Several disorders with abnormalities of neutrophil function are described in the following sections.

Chronic granulomatous disease

CGD is a rare primary inherited immunodeficiency syndrome usually diagnosed in early childhood and linked to mutations in genes encoding protein components of the NADPH oxidase system. In CGD, neutrophils and monocytes are unable to generate the respiratory burst that generates superoxide, the precursor to hydrogen peroxide and other reactive oxygen derivatives needed for killing of engulfed microbes. The disorder is characterized by recurrent bacterial and fungal infections affecting the skin, lungs, and bones, along with the development of granulomatous inflammatory responses in lymph nodes, gut, and other tissues.

The mutations responsible for CGD can be inherited in either an X-linked or autosomal recessive manner. About two-thirds of CGD cases are due to mutations affecting the X-linked gene CYBB, which encodes the gp91phox component of the oxidase complex. The remaining cases involve mutations of autosomal genes encoding other proteins participating in the oxidase complex.

The diagnosis of CGD is established by a typical clinical history and by laboratory testing demonstrating an abnormal neutrophil oxidative burst by histochemistry (nitrotetrazolium blue test) or flow cytometry (dihydrorhodamine assay). Genetic testing for both X-linked and autosomal recessive CGD is available.

Treatment of CGD consists of prophylactic antibiotics, antifungal agents, and prompt aggressive treatment for specific infections. Chronic treatment with interferon-γ reduces the incidence of bacterial and fungal infections by ~70%. HSCT, although curative, generally is reserved for patients in whom the clinical course or specific mutation portends a poor outcome and is a high-risk procedure in CGD patients. Gene therapies using lentiviral vectors are under development.

Leukocyte adhesion deficiency

Leukocyte adhesion deficiencies are very rare autosomal recessive disorders manifested by delayed wound healing, recurrent bacterial infections, and neutrophilia. There are 3 distinct types of LAD, all associated with impaired neutrophil chemotaxis and emigration from the blood to sites of infection. Mutations in β_2-integrin (CD18) (type 1), genes necessary for generation of selectin ligands (type 2), or other genes impacting on integrin function (type 3) have been implicated. In addition to lack of neutrophil function, patients with LADIII also have a bleeding diathesis due to a defect in integrin function on platelets. Definitive treatment of LAD requires allogeneic HSCT, with a recent study reporting a 5-year survival of 75%.

Myeloperoxidase deficiency

Myeloperoxidase (MPO) deficiency is the most common disorder of phagocytes, with 1 in 4000 individuals having a complete deficiency of MPO. It is inherited in an autosomal recessive fashion and is due to mutations of the *MPO* gene. MPO is a primary granule enzyme that catalyzes the conversion of H_2O_2 to hypochlorous acid and other toxic intermediates that greatly enhance polymorphonuclear neutrophil microbicidal activity. The diagnosis can be made with histochemical assays or flow cytometry for MPO in neutrophils. Of note, most patients (95%) with MPO deficiency are asymptomatic, surprising given the loss of enzyme activity. An increase in mucocutaneous infections with *Candida* strains has been reported, particularly in patients with concurrent diabetes mellitus. There is no specific treatment.

Hyperimmunoglobulin E syndrome

Hyperimmunoglobulin E syndrome (HIES; previously known as Job syndrome) is characterized by defective neutrophil chemotaxis, defective T-helper function, mild neutropenia, recurrent infections of the skin, sinuses, or lungs, eczema, and elevated serum IgE levels. Autosomal dominant HIES (60% to 70% of cases) is due to heterozygous mutations in *STAT3*. Autosomal recessive HIES is most commonly due to mutations in *DOCK8*. Patients with *DOCK8* mutations lack the nonimmunologic features of *STAT3*-HIES and instead are characterized by a high incidence of atopic conditions in addition to eczema

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and recurrent cutaneous viral infections with herpes simplex, human papilloma, and molluscum contagiosum viruses. They also are at markedly high risk of human papillomavirus–associated squamous cell carcinomas, Epstein-Barr virus–associated Burkitt lymphoma, and diffuse large B-cell lymphoma. The cornerstone of treatment for HIES is antibacterial, antifungal and, for *DOCK8*-HIES, antiviral prophylaxis. HSCT is curative for *DOCK8*-HIES and, given the severity of the disease and associated mortality, should be considered early.

Chédiak-Higashi syndrome

Chédiak-Higashi syndrome (CHS) is a rare autosomal recessive syndrome linked to mutations in the *LYST* gene and characterized by severe immunodeficiency, mild neutropenia, functional neutrophil defects, partial albinism, mild bleeding diathesis, and neurologic defects. The pathognomonic feature of CHS is the presence of giant inclusion bodies in virtually all granulated cells, particularly neutrophils (Figure 15-2). The majority of patients progress to an accelerated phase characterized by a nonclonal lymphohistiocytic infiltration of multiple organs. The loss of LYST protein disrupts vesicular trafficking, leading to hypopigmentation and abnormal granule and lysozyme formation, impairing multiple functions of immune cells and platelets. Treatment of CHS and other related vesicular transport syndromes is largely supportive or, in severe cases, allogeneic HSCT.

KEY POINTS

- Genetic disorders affecting neutrophil function are rare causes of recurrent infections, unexplained fever, and inflammation in children with normal or high neutrophil counts.
- CGD results from mutations in genes encoding components of NADPH oxidase, required for killing of microorganisms.
- LAD results from mutations in genes encoding adhesion molecules such as integrin, impairing tissue entry.

Autoinflammatory diseases

Autoinflammatory diseases, also called periodic fever syndromes, are a group of rare genetic disorders characterized by recurrent episodes of unprovoked inflammation in the absence of infection. The most common and prototypical autoinflammatory disease is familial Mediterranean fever (FMF). FMF usually presents in early childhood and is characterized by sporadic paroxysmal attacks of fever, serosal inflammation (such as peritonitis), and neutrophilia. These attacks generally last 1 to 3 days and then resolve spontaneously. FMF is inherited as an autosomal recessive disorder and mainly occurs in populations from the Mediterranean basin. Mutations in the *MEFV* gene, which encodes the protein pyrin, appear to cause unpredictable episodes of neutrophil overactivity and tissue infiltration. Because the chronic, recurrent inflammatory attacks also cause persistent elevations of serum amyloid A protein, patients with FMF are at high risk of developing complications of amyloid A amyloidosis. Colchicine prevents clinical attacks and tissue amyloid deposition in most patients with FMF. Rare patients with severe refractory disease have undergone successful HSCT.

FMF must be distinguished from other autoinflammatory diseases, of which there is an ever-increasing number. Hyper-IgD syndrome (also known as mevalonate kinase deficiency) is another rare autosomal recessive autoinflammatory disease and is associated with mutations in the mevalonate kinase gene, *MVK*. The tumor necrosis factor (TNF) receptor–associated periodic syndrome (TRAPS) is an autosomal dominant disorder associated with mutations in the gene-encoding TNF receptor 1, *TNFRSF1A*. Cryopyrin-associated periodic syndromes are a group of autosomal dominant inherited disorders that are caused by mutations of a pyrin-like protein called NALP3, encoded by the *CIAS1* gene. Although neutrophils are not the primary mediators of pathogenesis in these non-FMF disorders, they share many clinical features with FMF and should be considered in the differential diagnosis of unexplained recurrent fever with noninfectious autoinflammation.

KEY POINTS

- Recurrent inflammation mimicking infection with repeatedly negative cultures is a hallmark of the autoinflammatory syndromes such as FMF.

Acquired and inherited disorders of histiocytes and dendritic cells

The histiocytoses represent a broad spectrum of disorders characterized by infiltration and accumulation of dendritic cells, macrophages, or monocyte-derived cells in a wide range of tissues and organs. The presentation may vary from mild, self-limited disease to life-threatening conditions. In 2016, the Histiocyte Society proposed a revised classification to include 5 major groups: (1) Langerhans-related also including Erdheim-Chester disease (ECD), (2)

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cutaneous and mucocutaneous, (3) malignant histiocytoses, (4) Rosai-Dorfman disease, and (5) hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS). Disorders falling within these groups that have hematologic manifestations or are treated by hematologists are discussed in this section.

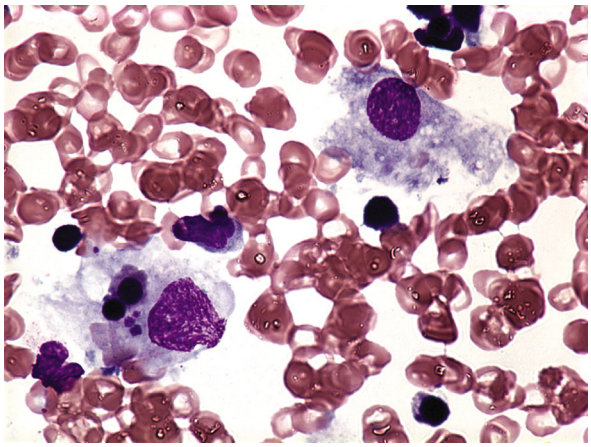
Langerhans-related histiocytoses

Langerhans cells are specialized dendritic cells found in the skin and mucosa. Langerhans-related histiocytosis (LCH) is a neoplastic disorder of dendritic cells associated with polymorphic cellular infiltration and damage at either unifocal tissue sites or in multiple organs and tissues. Although the dendritic cells in LCH expresses similar markers to skin Langerhans cells, they are believed to originate from a distinct myeloid dendritic cell precursor. Histologically, LCH lesions contain a mix of characteristic Langerhans cells in a background of eosinophils, neutrophils, and lymphocytes (Figure 15-3).

Mutually exclusive somatic mutations have been identified in >70% of patients with LCH, most commonly the *BRAF* V600E mutation. Even in patients without mutations identified, excess MEK and ERK phosphorylation are seen in virtually 100% of tumors, suggesting that activation of extracellular signal-regulated kinases drive LCH pathogenesis.

Patients with LCH are categorized as having either uni- or multifocal involvement of a single organ system (SS-LCH) or multiple systems (MS-LCH). SS-LCH most commonly involves bone and, less commonly, skin, lymph nodes, and lung (often in smokers). Usual presentations of limited disease relate to the site of involvement and include progressive bony pain or swelling, skin rash, ear drainage, dyspnea, cough, and pneumothorax. Diabetes insipidus may result from intracranial extension of craniofacial bone lesions and is the most common CNS manifestation, occurring in up to 30% of patients. MS-LCH most commonly occurs in children and presents with combinations of bony or soft tissue masses along with fever, rash, gingival swelling, cough or dyspnea, tooth loss, hepatosplenomegaly, lymphadenopathy and cytopenias.

Figure 15-3 Hemophagocytic lymphohistiocytosis. BM aspirate demonstrating phagocytic histiocytes with ingested platelets and RBC precursors. Source: ASH Image Bank, image 3502.



Treatment of LCH is based on the extent and activity of the disease. SS-LCH confers a good prognosis and frequently requires minimal or no treatment. Bony or soft tissue SS-LCH can be treated with surgical resection, local irradiation, or injection of steroids. Limited skin disease often responds to topical steroids, nitrogen mustard, or psoralen and ultraviolet A light therapy. Management of lung disease includes discontinuation of smoking; treatment with prednisone, vinblastine, and methotrexate; and immunosuppressive agents. Disease-free survival with limited or local LCH exceeds 95%; however, recurrences are common, and some patients require multiple courses of treatment to be cured.

MS-LCH and SS-LCH with multifocal involvement or involvement of critical anatomic sites are treated with systemic therapy, including vinblastine and prednisone. Small case series have shown activity of *BRAF* inhibitors. Involvement of the hematopoietic system, spleen, liver, and lung are considered high risk, with a mortality of ~20% compared with <5% for patients without high-risk features.

Erdheim-Chester disease is the second major class of Langerhans-related histiocytoses. Historically, ECD was classified as a non–Langerhans cell histiocytosis; however, recent advances have revealed that the majority of ECD cases bear the same spectrum of mutations seen in LCH, including *BRAF* V600E in more than 50%, leading to reclassification of ECD as a myeloid neoplasm.

ECD is most common in adult men, although rare pediatric cases have been reported. It is characterized by tissue infiltration by foamy or lipid-laden histiocytes with associated fibrosis. ECD histiocytes are positive for CD68 and CD163 and, in contrast to LCH, are negative for CD1a and langerin and only rarely positive for S100. Sites of involvement may include the skeleton, retroperitoneum, skin, CNS, heart, lungs, and less commonly, lymph nodes, liver, and spleen. More than 80% of patients have bilateral and symmetric diaphyseal and metaphyseal osteosclerosis of the legs, which is best visualized by bone scan or positron emission tomography. Importantly, even in the presence of highly suggestive clinical and radiographic findings, biopsy

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is required to confirm the diagnosis and determine *BRAF* mutational status, given potential targeted therapeutic options for *BRAF*V600E-mutated disease.

Interferon-α has been associated with improved survival and is considered first line therapy for most ECD patients. In addition, the *BRAF* V600E inhibitor vemurafenib is approved for ECD patients with *BRAF*V600E-mutated disease. Response rates are high (~90%) and sustained on therapy, while treatment withdrawal is associated with relapse in the majority of cases. Because of the risks of adverse side effects, vemurafenib is currently recommended for those patients with *BRAF* V600E mutation who have moderate to severe disease or who have mild disease refractory to interferon-α or other conventional therapy.

Malignant histiocytoses

The group of malignant histiocytoses includes sarcomas of histiocytic, interdigitating dendritic cells, Langerhans cells, or cells of indeterminate origin. Histiocytic sarcomas (HSs) are rare, with only a few hundred cases reported, most commonly in adults. HS can occur as an isolated disease (primary HS) or in the context of other hematologic neoplasms (secondary HS), such as follicular lymphoma, myelodysplasia, or acute lymphoblastic leukemia. It is not unusual that secondary HS and the underlying hematologic malignancy are found to be clonally related. It is important to differentiate secondary HS from myeloid sarcomas (leukemic infiltration of extramedullary sites).

Patients usually present with constitutional symptoms, but clinical presentation can vary based on site of organ involvement. Most common sites are the gastrointestinal tract and skin, but presentation can be multifocal, with involvement of other soft tissue sites. Diagnosis is based on biopsy of the involved tissue. Currently there is no standard treatment for HS. Depending on presentation and extent of organ involvement, surgical resection, radiotherapy, or systemic chemotherapy can be considered; enrollment to clinical trials is encouraged.

Rosai-Dorfman disease

Sinus histiocytosis with massive lymphadenopathy, also known as Rosai-Dorfman disease, is a nonmalignant proliferation of histiocytes within lymph node sinuses and lymphatics in extranodal sites. Emperipolesis of intact lymphocytes and plasma cells by histocytes is a hallmark. The condition most commonly occurs in children and young adults and presents as massive, painless, bilateral lymph nodes in the neck with fever. Although spontaneous resolution is observed in most cases, extranodal involvement often requires treatment, relapses can occur, and the condition occasionally can be fatal. There is no standard treatment approach, and therapies employed have included surgery, corticosteroids, radiation, thalidomide, or cytotoxic agents including vinca alkaloids and purine nucleoside analogues.

Emerging data indicate the presence of activating mutations in the MAPK/ERK pathway in a subset of juvenile xanthogranuloma and Rosai-Dorfman disease cases, linking these non–Langerhans cell histiocytoses with the Langerhans-related histiocytoses through common dysregulated cellular signaling.

Hemophagocytic lymphohistiocytosis and macrophage activation syndrome

CLINICAL CASE

A 9-month-old girl is admitted to the hospital after presenting with fever of 40.5°C, sore throat, and lethargy. Over the course of the next 48 hours, the child continues to have high fevers despite broad-spectrum antibiotics and develops progressive splenomegaly and pancytopenia. Laboratory data are also notable for a markedly elevated ferritin level of 24,000 ng/mL (normal 476 ng/mL) and hypofibrinogenemia. A BM biopsy reveals marked histiocyte hyperplasia with hemophagocytosis. She begins treatment with dexamethasone and etoposide. Mutational testing reveals the presence of a homozygous mutation in the *PRF1* gene.

Hemophagocytosis is the histologic finding of activated macrophages engulfing leukocytes, erythrocytes, platelets, and their precursor cells. Hemophagocytosis may be observed in a variety of conditions, including hemolytic anemias, infections, and malignancies. It is also a principal feature of hemophagocytic lymphohistiocytosis, a clinical syndrome characterized by fever, pancytopenia, and splenomegaly that results from the abnormal activation and proliferation of cytotoxic T lymphocytes and tissue macrophages (Figure 15-4). The major pathophysiologic abnormality in HLH is the high production of inflammatory cytokines with abnormal T-cell activation. Severe impairment in NK cell activity and cytotoxic T-cell function are also characteristic of the syndrome.

HLH most often occurs in infants and toddlers but may also be observed in children and adults of all ages. It may occur either as an inherited or acquired disorder (Table 15-4). Familial hemophagocytic lymphohistiocytosis (FHL) classically presents in infancy and early childhood with an estimated incidence of

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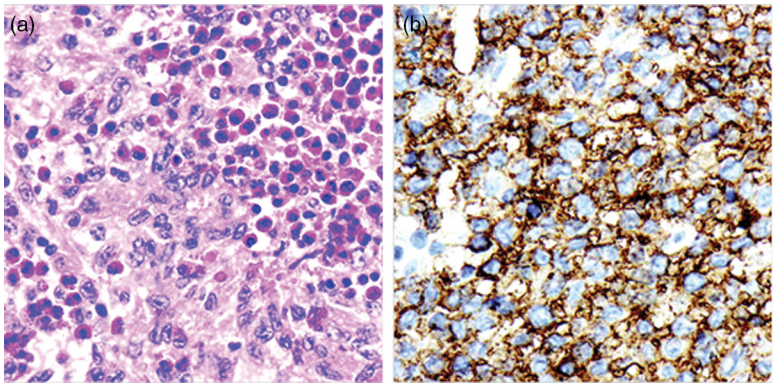

Figure 15-4 Langerhans cell histiocytosis. (A) Hematoxylin-eosin stain demonstrating Langerhans cell infiltrate. Cells have abundant eosinophilic cytoplasm with variably shaped nuclei ranging from cleaved, grooved, folded, indented, and even lobated. Clusters of eosinophils surround the infiltrate. (B) CD1a immunohistochemistry staining of Langerhans cells. Source: ASH Image Bank, images 3461 (A) and 3465 (B).

approximately 1 in 50,000. FHL is caused by autosomal recessive mutations in genes that encode critical components of the granule exocytosis pathway, which enable NK cells and cytotoxic T lymphocytes to induce apoptosis in target cells. Disease manifestations in inherited forms of HLH are frequently triggered by infection. Multiple gene defects have been linked to FHL subtypes, all resulting in impaired cytotoxic pathways in T cells, with secondary proliferation and activation of immune cells. The most common is FHL-2, caused by mutations in *PRF1*, which encodes perforin, the major component of the synapse between the effector lymphocyte and a target cell through which cytolytic contents are released to initiate cell death. FHL-3, FHL-4, and FHL-5 are caused by mutations in the Munc13-4 (*UNC13D*), syntaxin 11 (*STX11*), and syntaxin binding protein 2 (*STXBP2*) genes, respectively. The mutation in FHL-1 is known to map to 9q21.3-q22, but the gene remains unknown.

Table 15-4 Hereditary and acquired causes of HLH

Primary HLH
Familial HLH
Chédiak-Higashi syndrome
Griscelli syndrome
XLP
XIAP deficiency syndrome
Hermansky-Pudlak syndrome type 2
GATA2 deficiency
Secondary HLH
Infections
Herpesvirus infection, particularly EBV, CMV, HHV-8, HSV
HIV
Parvovirus, adenovirus, hepatitis virus
Bacterial, rickettsial, fungal, and spirochete-associated infections
Malignancy
AML, MDS, lymphomas, multiple myeloma
Metastatic carcinoma, metastatic melanoma
Autoimmune diseases (macrophage activation syndrome)
Other immunodeficiency states
Posttransplant
Cytotoxic or immunosuppressive therapy
Postsplenectomy

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV-8, human herpesvirus 8; HSV, herpes simplex virus.

In addition to FHL, a clinical HLH syndrome can also occur in the context of various other inherited primary immune deficiency syndromes and may be the presenting manifestation. Presumably the link with the hemophagocytic phenotype may be an ineffective primary immune response leading to diffuse immune activation.

Acquired HLH syndrome, also known as reactive hemophagocytic syndrome or secondary HLH (sHLH), can affect adults and children and is usually associated with an underlying infection (often viral), hematologic (particularly lymphoma) or (less commonly) nonhematologic malignancy, autoimmune or rheumatologic disorders, HIV disease (with or without opportunistic infections), posttransplantation immunosuppression, or other immunocompromised states. The pathophysiology of sHLH appears to be similar to that of FHL, except that

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the underlying predisposing disorder is primarily responsible for the dysregulation of T and NK cells, resulting in diffuse secondary histiocyte activation.

The clinical presentation, laboratory features, and histopathology of inherited and acquired HLH are similar. HLH should be considered in the differential diagnosis in patients who develop multiorgan dysfunction in the setting of fever, unexplained progressive pancytopenia, and hepatosplenomegaly. Lymphadenopathy, rash, and liver abnormalities may be present. Neurologic symptoms due to central nervous system involvement are present in one-third of patients. Laboratory findings include elevated ferritin, liver enzymes, triglycerides, and soluble interleukin-2 receptor alpha (sCD25 or sIL-2R) levels; decreased NK cell cytotoxic activity; and coagulation abnormalities. A BM or other impacted tissue biopsy is helpful to identify histiocytic hyperplasia and hemophagocytosis of nucleated cells and exclude malignancy or identify an infectious trigger for HLH. Hemophagocytosis, however, is highly variable and may not be observed early in the clinical course. If hemophagocytic activity is not proven at the time of presentation, further search for hemophagocytic activity is encouraged but not mandatory for diagnosis if other markers are consistent with HLH. Diagnostic criteria for HLH have been established by the Histiocyte Society (Table 15-5). At least 5 of 8 clinical criteria or the presence of either familial disease or one of the known genetic abnormalities is required for diagnosis of HLH.

Table 15-5 Diagnostic criteria for HLH

The diagnosis of HLH can be established if 1 of either item 1 or 2 is fulfilled: 1. A molecular diagnosis consistent with HLH 2. Diagnostic criteria for HLH fulfilled (5 out of the following 8 criteria)
Fever
Splenomegaly
Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood): Hemoglobin <90 g/L (in infants <4 weeks: hemoglobin <100 g/L) Platelets $<100 \times 10^9$/L Neutrophils $<1.0 \times 10^9$/L
Hypertriglyceridemia and/or hypofibrinogenemia: Fasting triglycerides ≥3.0 mmol/L (ie, ≥265 mg/dL) Fibrinogen ≤1.5 g/L
Hemophagocytosis in BM, liver, lymph nodes or spleen
Low or absent natural killer cell activity (according to local laboratory reference)
Ferritin ≥500 μg/L
Soluble CD25 (ie, soluble IL-2 receptor) ≥2400 U/mL

Although less severe sHLH may resolve after treatment of the underlying condition or with a short course of immunosuppression, untreated FHL is uniformly fatal within 1 to 2 months. Given it generally takes time to differentiate sHLH from FHL, early intervention is advocated for critically ill or deteriorating patients. The HLH-94 protocol is the current standard of care. It consists of an initial 8 weeks of dexamethasone and etoposide followed by a continuation phase for those patients with familial, relapsing, or severe and persistent disease consisting of cyclosporine A with pulses of etoposide and dexamethasone until an acceptable donor is identified for HSCT. In refractory, recurrent or progressive primary HLH, treatment with emapalumab, a monoclonal antibody that binds and neutralizes interferon-γ, should be considered. If a secondary "trigger" is identified, specific therapy against a specific infection, autoimmune disease, or malignancy is appropriate along with immune suppression.

Results of the HLH-94 trial demonstrated a 3-year survival rate of 51%, with comparable outcomes for FHL and sporadic HLH. Modifications to this protocol were tested in HLH-2004; however, this was not found to be beneficial, and, therefore, HLH-94 remains the standard of care. A single-center retrospective analysis of FHL patients treated with anti-thymocyte globulin, prednisone, maintenance cyclosporine, and intrathecal methotrexate and corticosteroids reported 82% short-term complete response rates in treatment-naïve patients.

Macrophage activation syndrome is considered to be a variation of sHLH and occurs in individuals with autoimmune disorders. The disorder is most frequently seen in systemic juvenile idiopathic arthritis (SJIA) but can also be observed in other rheumatologic conditions, including SLE and Kawasaki disease. Like other forms of HLH, MAS is characterized by fever, hepatosplenomegaly, cytopenias, and coagulopathy with the expansion of macrophages and T cells, as well as decreased cytotoxic T and NK cell function. Approximately 10% of individuals with SJIA can develop life-threatening MAS, although it is believed that a much higher percentage may have a milder or subclinical form. Although MAS resembles HLH, diagnostic criteria for HLH may not apply because some features, such as hyperferritinemia, lymphadenopathy, and splenomegaly, often are present during a flare of the underlying rheumatologic disease. MAS generally responds to high-dose corticosteroids alone or in combination with cyclosporine.

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KEY POINTS

- LCH and ECD are a clonal dendritic cell disorders that can present with involvement of a single tissue (usually the bone) or multiple tissues and organs and are linked to activation of ERK pathways, often due to *BRAF* mutations.
- HLH results from activation and proliferation of tissue histiocytes resulting from cytotoxic lymphocyte dysregulation, with severe multisystem clinical consequences and macrophage engulfment of hematopoietic cells.
- HLH may present in young children with an inherited predisposition (eg, due to perforin gene mutations) or in children and adults with acquired disorders of immune regulation due to infection, autoimmune disorder, malignancy, or acquired immunodeficiency states.

Lysosomal storage diseases

Lysosomal storage diseases are a collection of approximately 50 genetically inherited disorders characterized by a deficiency or defect in 1 or more specific lysosomal enzymes. These disorders lead to an accumulation of undigested material inside the lysosome, leading to cell degeneration and accumulation of macromolecules in various tissues and organs of the body and resulting in organ dysfunction. Many present in infancy or early childhood with profound progressive neurologic abnormalities in addition to cytopenias (for example, Niemann-Pick disease [NPD]). Gaucher disease represents a subtype of lysosomal storage diseases, also known as sphingolipidoses or lipid storage disorders, in which undigested lipids accumulate in the lysosome-rich cells of the monocyte or macrophage system. Gaucher disease is of particular importance to hematologists because type 1 patients most often present with cytopenias and hepatosplenomegaly and are often managed by hematologists.

Gaucher disease

CLINICAL CASE

A 23-year-old man from Ukraine presents with a several-month history of easy bruising, worsening fatigue, and hip pain. On physical examination, the patient is noted to be pancytopenic, with marked hepatosplenomegaly. A BM biopsy reveals the presence of lipid-laden macrophages consistent with Gaucher cells infiltrating the marrow. Leukocyte glucocerebrosidase is reduced to <10% of normal levels.

Clinical, epidemiologic, and genetic features

Gaucher disease is the most common lysosomal storage disease, resulting from deficiency of the glucocerebrosidase enzyme, which normally hydrolyzes glucocerebroside resulting from processing of senescent cells. This metabolite accumulates in the cytoplasm of macrophages in the BM, liver, spleen, and other tissues, resulting in a diagnostic wrinkled-paper appearance of these Gaucher cells (Figure 15-5).

Gaucher disease is an autosomal recessive and relatively common disorder, with an incidence of approximately 1 in 75,000 births, much higher in Ashkenazi Jewish populations. The disease is divided into 3 clinical subtypes based on pattern and severity of neurologic involvement. Type 1 (nonneuropathic) is most common (90% of all patients), has variable clinical presentation with onset of symptoms from 2 years of age to late adulthood, and is associated with the highest residual enzyme activity. Symptoms consist of hepatosplenomegaly, cytopenias, and bone deformation (flaring of the ends of the long bones and cortical thinning) and pain. Type 2 (acute neuronopathic) is associated with the lowest enzyme activity and results in progressive fatal neurologic deterioration beginning in infancy. Type 3 (subacute neuronopathic) falls between types 1 and 2 in incidence, enzyme activity, and

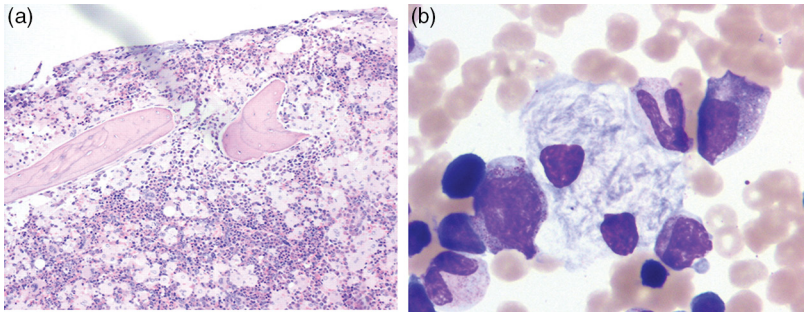

Figure 15-5 Gaucher disease. (a) Proliferation of benign-appearing macrophages with interspersed normal hematopoietic elements. (b) High-power view of BM aspirate demonstrating a Gaucher cell, an abnormal macrophage with the characteristic "wrinkled-paper" cytoplasm. Source: ASH Image Bank, images 2711 (a) and 2709 (b).

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clinical severity. Hematologists would likely only diagnose and treat Type 1 patients.

The diagnosis of Gaucher disease can be established by enzyme assay for glucocerebrosidase activity in leukocytes, fibroblasts, or urine and should be decreased to 0% to 30% of normal in symptomatic patients. Patients with Gaucher disease have an increased risk of monoclonal gammopathies and multiple myeloma, and some have paraproteins reactive with the elevated glycosylceramides characterizing Gaucher disease. Both patients with Gaucher disease and carriers have a markedly elevated risk of Parkinson disease due to unclear pathophysiologic pathways linking lysosomal processing, mitochondrial function, and aggregate formation in the brain.

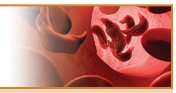
Treatment

Enzyme replacement therapy (ERT) is the mainstay of treatment for the nonneurologic manifestations of Gaucher disease. Imiglucerase is a recombinant glucocerebrosidase modified with mannose sugars to improve uptake and trafficking to the lysozymes of macrophages. ERT administered every 2 weeks normalizes cytopenias and reduces organomegaly within 6 to 12 months, although skeletal symptoms improve more slowly. Because glucocerebrosidase does not cross the blood-brain barrier, ERT has limited utility in the neuropathic forms of the disease.

A completely different treatment approach, termed oral substrate reduction (OSR) therapy, has been developed as an alternative to long-term parenteral ERT. Miglustat and eliglustat both inhibit glucosylceramide synthase, a key enzyme upstream of glucocerebrosidase, thereby reducing the substrate for the missing or dysfunctional glucocerebrosidase enzyme and decreasing toxic glucocerebroside accumulation. In clinical studies, improved platelet counts, decreased spleen and/or liver volume, and modest improvements in hemoglobin levels were achieved with OSR. OSR is usually reserved for patients unable to tolerate ERT or those with mild disease.

Niemann-Pick disease

NPD is an autosomal recessive lysosomal storage disorder caused by mutations in the sphingomyelin phosphodiesterase 1 (*SMPD1*) gene, resulting in deficient sphingomyelinase activity and accumulation of sphingomyelin. Cytopenias and hepatosplenomegaly are common presenting manifestations to hematologists. Patients with type A present in early childhood and die of profound neurologic abnormalities within several years. Milder type B patients may present later in childhood or adulthood and, importantly, lack the neurologic feature observed in patients with type A NPD. The histologic hallmark of NPD is tissue accumulation of histiocytes filled with lipid droplets of uniform size, giving these foam cells a "mulberry-like" or "honeycomb-like" appearance. Currently, no specific treatment exists for NPD.



KEY POINTS

- Gaucher disease is a lysosomal storage disorder caused by mutations in the glucocerebrosidase enzyme, leading to abnormal accumulation of glucocerebroside in tissue macrophages, resulting in hepatosplenomegaly, cytopenias, and skeletal disorders.
- ERT and substrate reduction therapy can reverse both nonhematologic and hematologic manifestations of Gaucher disease.

Inherited bone marrow failure syndromes

Although the inherited BM failure syndromes are rare disorders, diagnosis with one of these syndromes has profound implications for medical management and treatment of the symptomatic patient, as well as implications for family members potentially at risk for disease or for genetic transmission. Features of IBMFS syndromes are summarized in Table 15-6. As detailed in the table, BM failure is often not the only feature of the underlying genetic condition, and skin, nail, musculoskeletal, urogenital, or other phenotypic abnormalities can help guide diagnosis. Marrow failure may even be absent or present later than other syndromic manifestations in some patients. Clinical presentations and disease severity may vary significantly between patients with the same disorder, due to differences in specific mutations, modifying genes, or environmental factors. Even syndromes eventually resulting in pancytopenia often first present with a single lineage abnormality, at times obscuring the underlying diagnosis.

Some IBMFS syndromes with variable penetrance and/or a milder phenotype may not be diagnosed in childhood. Some patients do not present with significant cytopenias before they develop MDS or full-blown AML. Thus, some adults presenting with BMF or hematologic malignancies have an underlying undiagnosed IBMFS, with implications for prognosis, treatment, and genetic counseling.

A careful family history is important to elicit in any patients presenting with AA, isolated cytopenias, MDS, or AML, particularly those less than 40 years of age, focusing

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on cytopenias, blood cancers, and nonhematologic pathologies associated with IBMFS (eg, liver or lung fibrosis associated with telomeropathies). Any family history or suggestive clinical findings should stimulate diagnostic targeted sequencing of IBMFS gene panels. Application of these panels to cohorts of patients with AA, MDS, or AML is uncovering germline mutations in patients not previously suspected to have an IBMFS, underscoring the challenge in making a diagnosis based on clinical features alone. IBMFS have been known for decades and can be categorized primarily based on their clinical phenotypes, with genetics aiding the diagnosis. In recent years, several clinically heterogeneous MDS/AML predisposition syndromes had been discovered. Some of these syndromes (ie, GATA2 deficiency, SAMD9/SAMD9L disorders) can mimic classic IBMFS during initial disease stage, presenting with hypocellular bone marrows and cytopenias.

Fanconi anemia

CLINICAL CASE

A 12-year-old boy presents to his primary care physician with pallor and bruising. His past medical history is remarkable only for an orchiopexy during the first year of life to correct an undescended testis. Pancytopenia is now noted. The patient and his parents do not report any medication or toxin exposures. On initial examination, the boy appears to be a normal prepubescent male. On closer examination, however, his thumbs appear underdeveloped, and patches of cutaneous hyperpigmentation are noted on his trunk. BM cellularity is only 10%; the aspirate shows hypocellular spicules and rare megakaryocytes, most of which are abnormal uninucleate forms. Cytogenetic studies are normal. Exposure of peripheral blood mononuclear cells to diepoxybutane (DEB) results in numerous chromosomal breakages, confirming a diagnosis of FA.

Definition

Fanconi anemia is a genetically and clinically heterogeneous disorder characterized by defective DNA repair, chromosomal fragility and breakage, abnormal hematopoiesis, pancytopenia, constitutional abnormalities, and markedly increased life-long risk of leukemia and solid tumors.

Epidemiology

FA is one of the most common of the inherited BM failure syndromes. The incidence of FA in the United States has been estimated at approximately 1 in 130,000 live births. It is more common among persons of Ashkenazi Jewish descent than among others.

Pathophysiology

A hallmark of cells from patients with FA is hypersensitivity to DNA damage induced by DNA crosslinking agents, such as DEB and mitomycin C (MMC). FA is a heterogeneous disease at the molecular level, with 22 FA genes identified to date, all encoding factors participating in complex DNA repair processes via the FA/BRCA pathway (Figure 15-6). Each of these genes, when biallelically mutated, can cause FA, except for *FANCB*, which causes X-linked recessive disease, and *FANCR/RAD51*, which has been associated with autosomal dominant disease. More than 75% of patients have mutations in *FANCA* or *FANCC*.

The cause of the progressive AA in FA has been thought to be due to the loss of HSPCs resulting from cumulative DNA damage. Recent studies suggest exacerbated p53/p21 DNA damage responses, sensitivity to formaldehyde produced during hematopoietic differentiation, and hyperactive MYC as pathophysiologic factors leading to HSPC impairment and depletion. There is also emerging evidence for dysregulation of transforming growth factor (TGF)-β and TNFα pathways. Additionally, FA hematopoietic progenitor cells are hypersensitive to interferon-γ, a known inhibitor of hematopoiesis, as well as to aldehydes.

Clinical features and diagnosis

FA is characterized by pancytopenia and congenital anomalies in the cutaneous, musculoskeletal, cardiac, and urogenital systems. Characteristic physical findings include short stature, microcephaly, intense patchy brown pigmentation of the skin (café au lait spots), and abnormalities of the radius, wrist, and/or thumb. Hemoglobin F levels are increased in FA, and almost 60% of patients develop signs of BM failure by age 20 years. Approximately 30% of patients with FA lack typical physical findings, and isolated marrow failure or development of a malignancy may be the first clinical manifestation of FA. Approximately 10% of patients with FA first come to clinical attention as young adults.

Chromosome breakage testing secures the diagnosis in most patients and entails analysis of chromosome aberrations (breaks and complex rearrangements known as radials) in phytohemagglutinin-stimulated peripheral blood lymphocytes cultured with and without DNA crosslinking agents such as DEB or mitomycin C. Results are reported as percentage of cells with chromosome aberrations in comparison to cells from a healthy donor (negative control) and from an individual affected by FA (positive control). The percentage of cells with chromosome breakage is increased dramatically in FA.

Diagnosis of FA may be complicated by the development of somatic mosaicism in lymphocytes. Somatic

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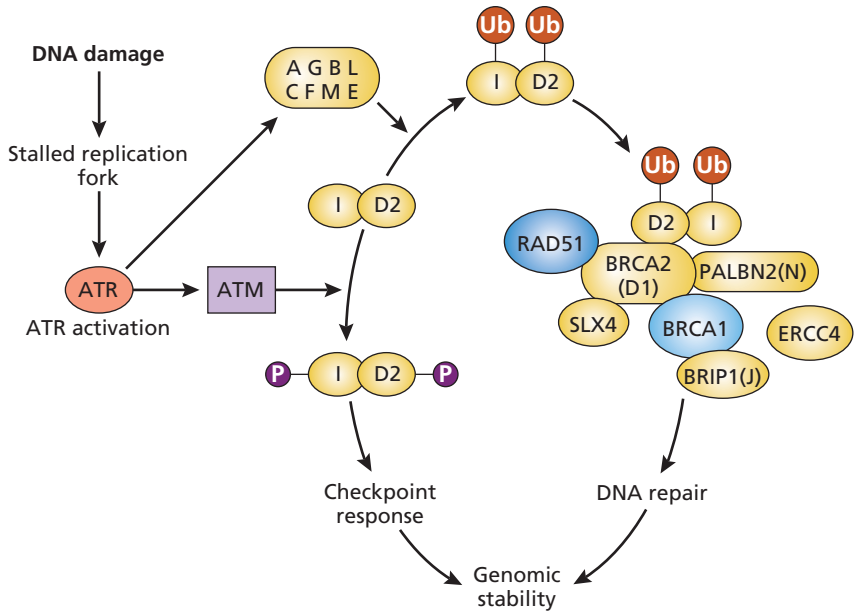

Figure 15-6 Fanconi anemia DNA repair pathway components. The FA core complex consists of 8 FA proteins (A, B, C, E, F, G, L, and M) and this together with ATR (ataxia-telangiectasia and RAD3 related protein) is essential for the ubiquitination-activation of I-D2 complex after DNA damage. Activated I-D2-Ub translocates to DNA repair foci, where it associates with other DNA damage response proteins, including BRCA2 and RAD51, and participates in DNA repair. The proteins mutated in different FA subtypes are shaded yellow.

mosaicism results from a genetic reversion (via recombination or compensatory base changes) of a mutant *FANC* gene allele to normal (non-FA), such that a subset of lymphocytes no longer exhibits increased chromosomal breakage in response to DEB or MMC. Because reversion to wild type confers a growth advantage over the non-reverted FA cells, the diagnosis of FA may be missed. In patients for whom there is a strong suspicion for FA, the diagnosis may be made by testing for chromosomal breakage in response to DEB or MMC using cultured skin fibroblasts obtained from a punch biopsy.

Complications of marrow failure are the most common causes of death in FA, but FA is also characterized by an increased incidence of malignancies. The relative risk for AML is increased 700-fold and MDS 6000-fold, with up to 40% of patients with FA developing MDS or AML by middle age, often in the context of a hypoplastic marrow and monosomy 7. The clinical significance of an abnormal marrow cytogenetic clone in the absence of morphologic dysplasia is not always clear, because some abnormal clones, for instance with gain of 1q, may be stable or even regress over time. However, deletion of 7/7q, gain of 3q, RUNX1 rearrangements and complex cytogenetic abnormalities herald rapid transformation and require urgent treatment decisions. Patients with FA are also at greatly increased risk for squamous cell carcinomas, in particular head and neck, esophageal, and vulvar/vaginal tumors. Hepatocellular carcinoma, peliosis hepatis, and hepatic adenomas occur with increased frequency, especially in patients treated with androgens. The risk of AML plateaus after the second decade of life, whereas the risk of solid tumors increases with age; in a competing risk analysis, 30% of patients with FA develop a solid tumor by age 48 years.

Treatment

The only potentially curative option for BM failure or MDS/AML in patients with FA is allogeneic hematopoietic cell transplantation. Because of the increased sensitivity of FA cells to DNA damage-inducing agents, in general, conditioning regimens that are radiation-free and deliver reduced doses of DNA crosslinking agents such as cyclophosphamide are required to avoid severe nonhematologic toxicity. For this reason, it is critical to identify patients with FA as having the condition before proceeding to HSCT. Patients with FA who present with MDS or AML without an observed BM failure phase may go unrecognized until the use of standard remission induction or transplantation conditioning regimens results in severe regimen-related morbidity or mortality.

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While HSCT corrects the hematopoietic defect, patient remain at risk for FA-related complications in other tissues, such as solid tumors. Moreover, some studies have suggested that HSCT in FA is associated with an increased risk of subsequent solid tumors, particularly in the setting of chronic graft-versus-host disease. Despite these limitations, HSCT from an unaffected HLA-identical sibling may be considered as the initial treatment of choice for patients with FA who present with BM failure. Outcomes of unrelated donor HSCT, while historically very poor, have substantially improved and approached that matched sibling transplants (5-year overall survival of 86% versus 94%, respectively) using FA-tailored conditioning regimens at transplantation centers with expertise in FA. Outcomes are better if transplantation occurs before the development of leukemia, so regular surveillance of the peripheral blood counts and BM is recommended in all FA patients.

Androgens may elevate the blood counts in a subset of patients with FA. Red blood cell counts are most often improved, although increases in platelet and neutrophil counts may also occur. The neutrophil count may also respond to G-CSF. Responses to androgens or G-CSF are often transient, and these drugs mainly serve as bridges to transplantation.

Because of the risk of nonhematologic cancers, patients with FA should undergo regular screening beginning in the late teenage years, including gynecologic examination for female patients after menarche. Regular dental care with examination for head and neck cancers is important. Liver ultrasound at least once yearly is recommended for patients on androgens. The exquisite sensitivity of patients with FA to the DNA-damaging effects of chemotherapy and radiation poses a formidable obstacle to the treatment of malignancies in these patients. The most successful treatment of solid tumors in FA results from early detection and complete surgical excision.

KEY POINTS

- FA is characterized by hypersensitivity to DNA damage due to germline mutations in 1 of at least 22 genes, diagnosed by DEB or MMC chromosome breakage studies.
- Most patients with FA develop signs of BM failure in childhood or adolescence, and many have physical stigmata including hyperpigmented skin patches and abnormalities of the thumb or wrist.
- Patients with FA are at high risk for MDS/AML and solid tumors.
- HSCT is the only curative option for FA-associated BMF or MDS/AML but requires attenuated conditioning regimens to avoid excess toxicity from chemotherapy and radiation.

Telomere biology disorders

CLINICAL CASE

A 16-year-old boy presents to his doctor with skin changes, nail abnormalities, and bruising. Examination shows he has significant nail dystrophy and reticulate skin pigmentation around the neck. Blood counts reveal moderate pancytopenia, and BM cellularity is found to be markedly reduced. Peripheral blood chromosomal breakage analysis following exposure to DEB is normal. Subsequent tests, however, show he has very short telomeres and a missense mutation in the *DKC1* gene, confirming a diagnosis of X-linked dyskeratosis congenita.

Definition

The telomere biology disorders (also referred to as telomeropathies or short telomere syndromes) encompass a spectrum of diseases which may present in early infancy to middle adulthood with clinically significant single- or multisystem involvement. While different names have been used to describe the various clinical presentations of TBDs (eg, classical dyskeratosis congenita [DC], Hoyeraal-Hreidarsson syndrome [HHS], or familial MDS), they all share the underlying molecular defect of abnormally short telomeres for age.

Clinical features

Patients with classical DC present with at least 1 feature of the classic mucocutaneous triad of abnormal skin pigmentation, nail dystrophy, and oral leukoplakia in childhood, but BM failure can be the first presenting feature of TBDs more generally, and classical DC mucocutaneous findings are seen in a minority of TBD patients, with some features not developing until adulthood, if at all. BM failure often develops before 20 years of age, with up to 80% of patients showing signs of BM failure by the age of 30 years. There is considerable variation between patients with respect to age of onset and disease severity, even within the same family, which can make diagnosis based on clinical features alone challenging.

Patients with TBDs are also at risk for pulmonary fibrosis (which is a common presenting feature in adult-onset TBS), cirrhosis, vascular complications (including arteriovenous malformations, gastrointestinal bleeding, and retinal vascular abnormalities), hepatopulmonary syndrome, and hematologic and solid malignancies, particularly head and neck squamous cell carcinoma but also anogenital and other gastrointestinal cancers. In addition, B and NK cell lymphopenia, but also T-cell dysfunction,

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can develop even in the absence of bone marrow failure and predispose to potentially life-threatening opportunistic infections in children and adults with TBDs. The main causes of mortality in TBD are BM failure (~60% to 70%), pulmonary disease (~10% to 15%), and malignancies (~10%).

Diagnosis

Telomere length testing is an important component in the diagnosis of TBDs as it is now available on a clinical basis, generally utilizing telomere flow-FISH to measure average telomere lengths in peripheral blood. Telomere length below the first percentile for age in lymphocyte populations is generally consistent with a diagnosis of a TBD.

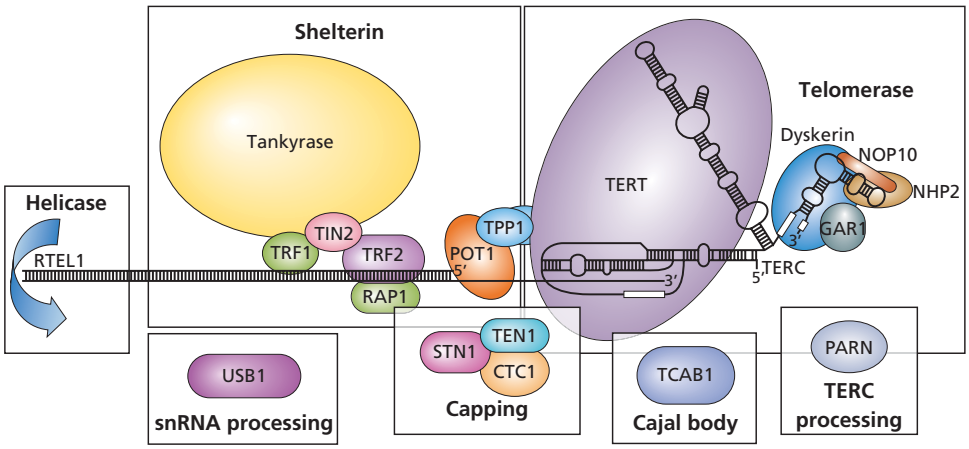
With advances in awareness of the clinical spectrum of TBDs and availability of telomere length testing, diagnosis in adults is increasing. This includes in patients with AA in the absence of the mucocutaneous triad characteristic of DC, MDS without a preceding diagnosis of AA, and rarely AML. In addition, 15% to 30% of patients with familial pulmonary fibrosis in the absence of cytopenias have been found to have TBDs, as well as some patients with seemingly sporadic disease. A personal or family history of AA in an individual with pulmonary fibrosis is highly predictive of an underlying TBD. Similarly, a personal or family history of pulmonary fibrosis in a person with AA should prompt consideration of a TBD.

Pathophysiology

Fourteen genes have been associated with the TBDs to date. Figure 15-7 shows the different components of the telomerase and shelterin complexes as well as other factors important in telomere maintenance. Telomerase is a specialized reverse transcriptase that adds a telomeric repeat to the end of the DNA strands after replication, essential to maintain telomere length in rapidly dividing cells, such as hematopoietic stem and progenitor cells and activated T cells. Without telomerase, telomeres shorten with each successive round of replication, and when a critically short length is reached, cells enter senescence. BM failure in patients with very short telomeres is thought to be driven by premature loss of HSPC.

Autosomal dominant, autosomal recessive, and X-linked recessive inheritance is reported. Early childhood onset and multisystem disease is most often associated with X-linked recessive mutations in *DKC1*, heterozygous de novo mutations in *TINF2*, and biallelic mutations in *RTEL1* and *TERT*. Adult presentation of hematologic, pulmonary, or liver disease is typically associated with heterozygous mutations in *TERT*, *TERC*, *RTEL1*, or *PARN*.

Figure 15-7 Cellular components important in telomere maintenance. A schematic representation of the telomerase complex (dyskerin, GAR1, NHP2, NOP10, TERC, and TERT), the shelterin complex, and their association with different categories of dyskeratosis congenita and related diseases. The minimal active telomerase enzyme is composed of of TERT, TERC (a nontranslated RNA), and dyskerin. PARN is involved in the processing of TERC, whereas dyskerin, GAR1, NHP2, and NOP10 are believed to be important for the stability of the telomerase complex. The shelterin complex is made up of 6 proteins (TIN2, POT1, TPP1, TRF1, TRF2, and RAP1) and is important in protecting the telomere. Mutations in components of the telomerase complex, the shelterin complex and related molecules, as occurs in different subtypes of DC and related disorders, result in telomere shortening.



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Treatment

BM failure is the main cause of premature mortality in TBDs. Androgens (oxymetholone or danazol) can produce improvement in hematopoietic function in approximately two-thirds of patients with DC respond to androgens; in some cases, the response can last several years and involve all lineages. A prospective study of adults with AA and underlying TBD demonstrated that danazol is associated with increases in telomere length in peripheral blood mononuclear cells. It is important to monitor for side effects (eg, liver toxicity). The concurrent use of androgens and G-CSF is not recommended due to reports of splenic peliosis and/or rupture in patients with DC receiving these treatments simultaneously.

The only option with curative potential for the hematologic abnormalities in TBDs is allogeneic HSCT. Historically, significant mortality was associated with HSCT in patients with DC, with the selection of conditioning regimen appearing to have an impact on patient survival. In the past, myeloablative conditioning regimens were associated with poor outcomes, particularly acceleration of liver and lung disease. The adoption of reduced intensity and nonmyeloablative regimens has allowed for durable engraftment with lower rates of transplant-related morbidity and mortality. Allogeneic HSCT from unaffected HLA-identical sibling donors have better survival rates than HSCT from alternative donors. Patients with DC need to be followed up long term for nonhematological complications such as pulmonary fibrosis, liver cirrhosis, vascular complications, and cancers, which represent the natural history of the disease and are not corrected by HSCT.

KEY POINTS

- TBDs are associated very short telomeres for age; and clinical presentations ranging from classical DC presenting in childhood with dystrophic nails, reticulated skin pigmentation, and oral leukoplakia in addition to BMF to adult-onset BMF alone.
- Nonhematologic features of TBDs such as pulmonary fibrosis and cirrhosis can develop later in life, and a family history of these disorders in a patient with BMF should stimulate testing for a TBD.
- Androgens can improve blood counts in some patients and potentially retard telomere loss, but the only curative treatment for TBD BMF is allogeneic HSCT.

GATA2 deficiency

CLINICAL CASE

A 35-year-old patient is diagnosed with AML (80% marrow blasts, trisomy 8, NPM1 mutation). At age 15 she was noted to have mild cytopenias with a moderately hypocellular marrow, not requiring any therapies. Her 6-year-old daughter presents a few months later with MDS and excess blasts (15%) and monosomy 7. Her B-cell count is low, and her T-cell CD4/CD8 ratio is decreased (0.6). Genetic testing reveals a heterozygous truncating GATA2 mutation in both mother and daughter, and both undergo HSCT from HLA-matched unrelated donors.

Clinical features and pathophysiology

Germ line heterozygous mutations in the *GATA2* gene, which encodes a zinc finger transcription factor required for hematopoiesis and lymphatic development, have been linked to 4 previously described overlapping inherited clinical phenotypes, specifically monocytopenia and mycobacterial infections (MonoMAC syndrome); dendritic cell, monocyte, B and NK cell lymphoid deficiency syndrome; primary lymphedema with MDS/AML (Emberger syndrome); and a subset of familial and/or pediatric MDS. Genetic studies uncovered mutations in the *GATA2* gene in all, and these entities are now designated GATA2 deficiency and represent the same underlying disorder with variable penetrance and severity. GATA2 deficiency is part of the new WHO category introduced in 2016 termed "myeloid neoplasms with germline predisposition" (Figure 15-8). Some of these additional disorders also often present with cytopenias (for example thrombocytopenia in *ETV6*, *RUNX*, and *ANKRD26* gene mutation carriers) before progressing to MDS/AML.

To date, more than 500 GATA2 deficiency patients have been reported in literature. Inheritance is autosomal dominant; however, clinical manifestations, even within the same family, can be extremely variable. The *GATA2* mutations result in haploinsufficiency due to loss of expression or protein function, with mutations found in both zinc finger and regulatory regions, as well as synonymous mutations causing RNA degradation.

Extrahematologic manifestations are present in at least half of reported patients and are variable, including congenital hearing loss, lymphedema, or autism spectrum disorders. Patients generally present to hematologist or immunologist in adolescence or early adulthood. Initial manifestations can be viral, bacterial (including

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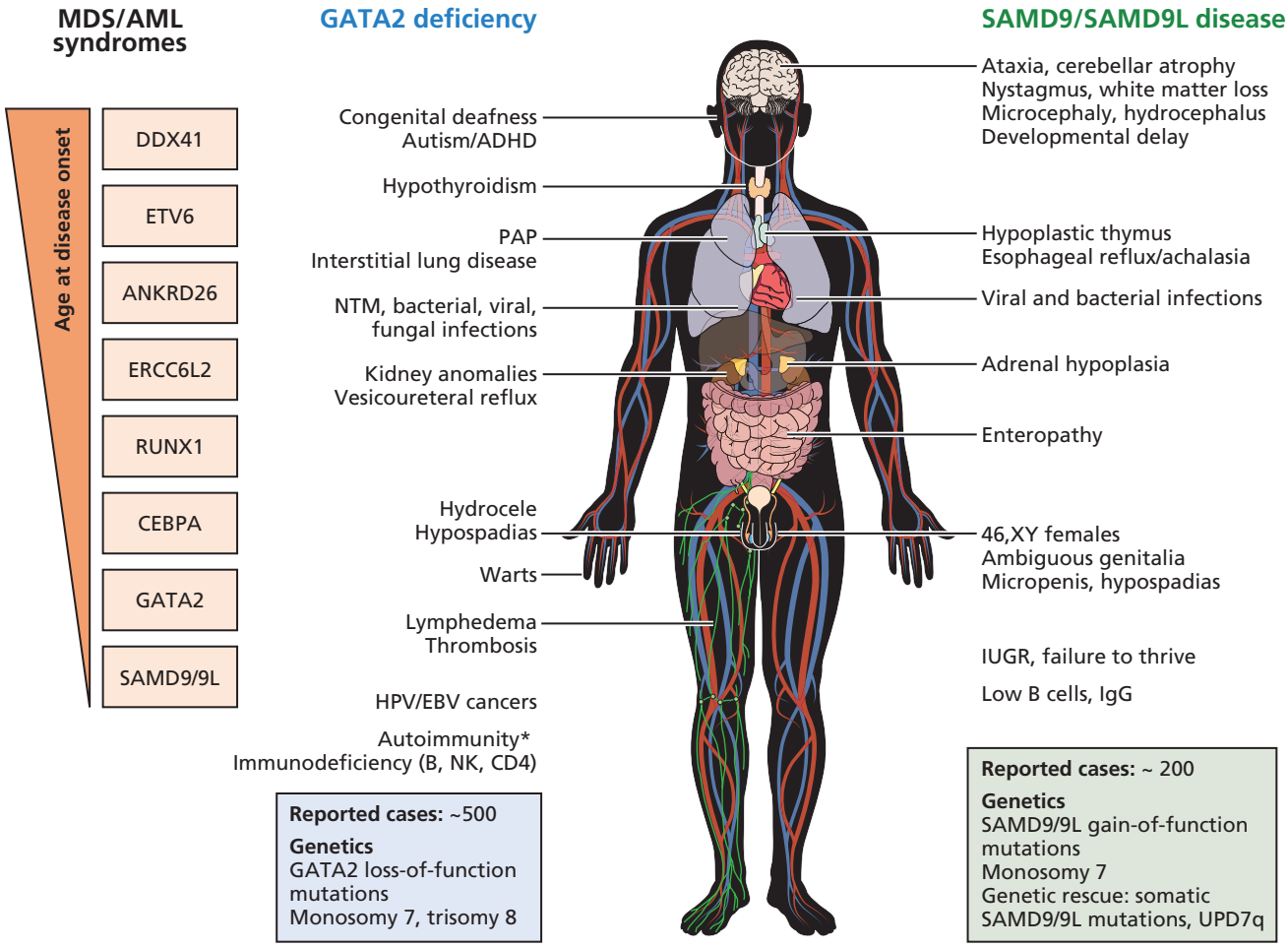

Figure 15-8 Clinical and genetic features of GATA2 deficiency and SAMD9/SAMD9L disease. The figure summarizes the protean clinical, laboratory, and genetic features of these IBMFDs, including predisposition to MDS/AML and average age of onset, compared to other myeloid malignancy predisposition syndromes.

mycobacterial), or fungal infections, with or without cytopenias, often with normal marrow morphology. Some present with MDS without prodromal cytopenias or infections.

Specific features in patients presenting with cytopenias or infections suggesting GATA2 deficiency include reduced peripheral blood monocytes (although monocytosis might be present in patients already progressed to MDS), low B and/or NK cell counts, inverted CD4/8 T-cell ratios, and marrow hypocellularity with dysplastic megakaryocytes and absent developing B cells (hematogones). Monosomy 7 and trisomy 8 are the most frequent cytogenetic abnormalities, and their presence often portends rapid progression to high-risk MDS and AML. *GATA2* mutations are the most a common germline cause of pediatric MDS, found in one-third of patients with monosomy 7. Median age at onset of MDS/AML is estimated to be ~20 years, and the lifetime penetrance for MDS/AML is very high (estimated at 90%). Additional clinical findings are shown in Figure 15-8 and Table 15-6.

Treatment

In addition to monitoring for infections and other non-hematological disease complications, serial blood counts and an annual BM evaluation including cytogenetics are generally performed, but individualized surveillance approaches are warranted. There are no specific or curative treatments other than allogeneic HSCT. Potential family donors must undergo *GATA2* sequencing, given variable clinical penetrance in many families. Development of high-risk cytogenetic aberrations

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Table 15-6 The inherited bone marrow failure syndromes

Syndrome	Median age at diagnosis (years)	Congenital features	Hematologic features	Malignancy risk	Key diagnostic features	Germline genetic cause and somatic mutations
Fanconi anemia	~6	Hyperpigmentation and café au lait spots, short stature, triangular face, abnormal thumbs/radii, microcephaly, abnormal kidneys, decreased fertility	Pancytopenia, hypocellular BM +/− dysplasia	MDS/AML (high risk), head and neck, gynecologic, rhabdomyosarcoma, nephroblastoma, liver, CNS cancers (in some subtypes)	Increased chromosome breakage in blood cells cultured with DNA crosslinking agents (DEB and MMC)	Germline: *FANCA, FANCC,* and *FANCG* account for 95% of cases. Somatic: *RUNX1* mutations and FA gene reversion mutations
Telomere biology disorders	~15	Classic triad (rare) of nail dystrophy, abnormal skin pigmentation and oral leukoplakia; pulmonary fibrosis, liver fibrosis, vascular abnormalities, esophageal strictures, early hair graying, cerebellar hypoplasia, retinopathy	Pancytopenia, hypocellular BM +/− dysplasia	MDS/AML (low risk); solid tumors including head and neck and anorectal carcinomas	Very short telomere length in peripheral blood using flow-FISH	Germline: *DKC1, TINF2, TERT, TERC,* and *RTEL1* account for ~60% of cases
GATA2 deficiency	~20 (MDS/AML)	Hearing loss, lymphedema, hydrocele, verrucosis, thrombosis, autism, attention deficit/hyperactivity	Variable cytopenias, hypocellular BM +/− dysplasia	MDS/AML (high risk)	Monosomy 7, der1;7, low monocytes, B/NK cells, reverted CD4/8 ratios	Germline: *GATA2* Somatic: MDS type mutations (*SETBP1*, *ASXL1 STAG2,* etc)
SAMD9/SAMD9L	Childhood	Ataxia (SAMD9L), adrenal hypoplasia and genital phenotypes (SAMD9)	As above	MDS/AML (moderate risk)	UPD7q, monosomy 7	Germline: *SAMD9 orSAMD9L*, with reversion in bone marrow cells in some cases Somatic: MDS type mutations (*SETBP1*, *ASXL1 STAG2*, etc)
Diamond-Blackfan anemia	<1	Short stature, abnormal thumbs, hypertelorism, cardiac septal defect, cleft lip or palate, short neck hypertelorism, cardiac septal defect, cleft lip or palate, short neck	Macrocytic anemia with reticulocytopenia	Colorectal carcinoma, osteosarcoma, breast cancer, MDS/AML	Elevated red cell adenosine deaminase (eADA), fetal hemoglobin (HbF); BM erythroid hypoplasia	Germline: *RPS19, RPL5, RPS26, RPL11, RPL35A,* and *RPS24* account for >90% of cases; *GATA1*, *TP53* (gain of function), *ADA2*
Congenital dyserythropoietic anemias	<1 to adulthood	CDA III: retinal abnormalities	Anemia, anisopoikilocytosis, iron hyperabsorption, hemolysis	None	BM dyserythropoiesis (type 1: binucleate, chromatin bridging; type 2: multinucleate; type 3: giant multinucleate	CDA I: *CDAN1* CDA II: *SEC23B* CDA III: *KIF23*

Table continues on next page

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Table 15-6 The inherited bone marrow failure syndromes *(continued)*

Syndrome	Median age at diagnosis (years)	Congenital features	Hematologic features	Malignancy risk	Key diagnostic features	Germline genetic cause and somatic mutations
Shwachman-Diamond syndrome	1	Short stature, exocrine pancreatic insufficiency with malabsorption	Neutropenia (leading), anemia, thrombocytopenia, AA	MDS/AML (high risk)	Low pancreatic isoamylase (after age 3 y) and trypsinogen (before age 3 y); low fecal elastase	Germline: *SBDS* accounts for ~90% of cases, also *SRP54*, *ELF1*, *DNAJC21* Somatic: *EIF6* and *TP53* mutations with MDS/AML
Severe congenital neutropenia	~3	None	Neutropenia, myeloid lineage maturation arrest in marrow	MDS/AML (moderate risk)	BM exam for promyelocyte arrest	Germline: *ELANE* most common, *HAX1*, *G6PC3*, *JAGN1*, *GFI1*, *VPS45A*, *TCRG1* Somatic: *CSF3R*, *RUNX1* with MDS/AML
Congenital amegakaryocytic thrombocytopenia	<1		Thrombocytopenia; decreased megakaryocytes initially, progression to pancytopenia	None	BM exam for megakaryocytes	Germline: *C-MPL*, *TPO*
MECOM-associated syndrome/ RUSAT	<1	Radioulnar synostosis, other skeletal defects, low B cells, hearing loss, cardiac and renal abnormalities	Thrombocytopenia with decreased megakaryocytes. hypocellular pancytopenia	Unknown	BM exam for megakaryocytes and cellularity	Germline: *MECOM*, rare patients with similar syndrome and *HOX11A*
Thrombocytopenia with absent radii syndrome	<1	Absent radii; abnormal ulnae or humeri; urogenital, cardiac and facial anomalies; cow's milk allergy	Thrombocytopenia present at birth and improving over time (often normal platelet counts in adults)	MDS/leukemia (rare)	BM exam for megakaryocytes	Germline: *RBM8A*

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involving chromosome 7 and some abnormalities considered low risk in sporadic MDS (eg, trisomy 8) or morphologic signs of transformation to MDS/AML are indication for prompt transplantation. Best HSCT outcomes are achieved in patients with less advanced disease.

SAMD9 and SAMD9L syndromes

SAMD9 and *SAMD9L* (*SAMD9/9L*) are paralogous genes on chromosome 7q and play roles in antiviral immunity and cell growth supression. Similar to GATA2 deficiency, *SAMD9/9L* mutations were discovered independently in patient cohorts with several different clinical phenotypes, including marrow failure and MDS/AML (Figure 15-5). *SAMD9* mutations were first linked with MIRAGE (myelodysplasia, infection, growth restriction, adrenal hypoplasia, genital phenotypes, and enteropathy) and *SAMD9L* mutations with ataxia-pancytopenia and CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature).

Despite their recent discovery, over 130 patients with germline, mostly missense gain-of-function *SAMD9/9L* mutations have been reported. The prevalence of germline *SAMD9/9L* mutations in pediatric MDS is high (estimated at 8%-15% of cases). Some patients present with cytopenias and a hypocellular BM, thus mimicking classical IBMFS. The clinical spectrum is broad; not only is there is overlap between *SAMD9* and *SAMD9L* mutation phenotypes, but there is also overlap with GATA2 deficiency (Figure 15-8).

Interestingly, in *SAMD9/9L* syndromes, there is preferential loss of the specific chromosome 7 that contains the mutant *SAMD9* or *SAMD9L* allele, thought to represent an escape mechanism from the growth-restrictive effects of the mutant proteins and improvement in BMF but also resulting in MDS. Alternative hematopoietic rescue events are seen in many patients, including additional loss-of-function mutations (thought to compensate for the germline mutation) or uniparental isodisomy 7q resulting in duplication of the wild type 7q arm. If no *SAMD9/9L* mutations are found in hematopoietic specimens despite a clinical phenotype consistent with SAMD9/9L disease, sequencing of germline tissue (fibroblasts) should be performed, as germline mutations might have very low allelic frequency (as low as <5%) in blood.

Similar to GATA2 deficiency, allogeneic HSCT is the only known treatment for *SAMD9/9L* patients with severe cytopenias or with MDS/AML. The results reported to date are encouraging.

KEY POINTS

- GATA2 deficiency patients can first present with hypocellular BMF, MDS with monosomy 7 and trisomy 8, immunodeficiencies and unusual infections, and/or deafness and lymphedema.
- *SAMD9* and *SAMD9L* gain-of-function mutations cause syndromes with variable BMF or MDS phenotypes and a range of congenital abnormalities.
- Reversion events via loss/additional mutations/uniparental disomy of the 7q chromosomal region carrying the mutant *SAMD9* and *SAMD9L* allele are common.

Shwachman-Diamond syndrome

Definition and clinical features

SDS is an autosomal recessive disorder characterized by exocrine pancreatic insufficiency and BM dysfunction with neutropenia as the most frequent cytopenia. Other features can include skeletal anomalies (short, flared ribs, metaphyseal dysostosis, short stature), pancytopenia, hepatomegaly, pancreatic lipomatosis, autism spectrum disorders, and intellectual disability. Signs of pancreatic insufficiency (malabsorption, failure to thrive) are apparent early in infancy, with pancreatic function improving in a subset of patients. The spectrum of hematological abnormalities includes neutropenia (~60%) and other cytopenias (~20% have pancytopenia).

Exocrine pancreatic insufficiency and hematological abnormalities are also seen in Pearson syndrome, a fatal multiorgan mitochondrial disease presenting in infancy with neurological, pancreatic, and BM abnormalities and is therefore important in the differential diagnosis of very young patients. Other differential disorders to be differentiated from SDS are cartilage hair hypoplasia syndrome and cystic fibrosis.

Pathophysiology

The majority (~90%) of patients with SDS have an autosomal recessive disorder due to biallelic mutations in the gene *SBDS*. The SBDS protein is involved in the joining of the 40S and 60S ribosomal subunits to form the 80S ribosome (Figure 15-9). Neutrophil chemotaxis defects are also observed in SDS and may contribute to infection risk. Recently, rare patients with SDS or an SDS-like syndrome lacking mutations in *SBDS* were found to have mutations in *SRP54*, *DNAJC21*, or *ELF1* genes.

Reported rates of transformation to MDS/AML range from 5% to 36%. An analysis of patients who received HSCT for MDS uncovered germline biallelic

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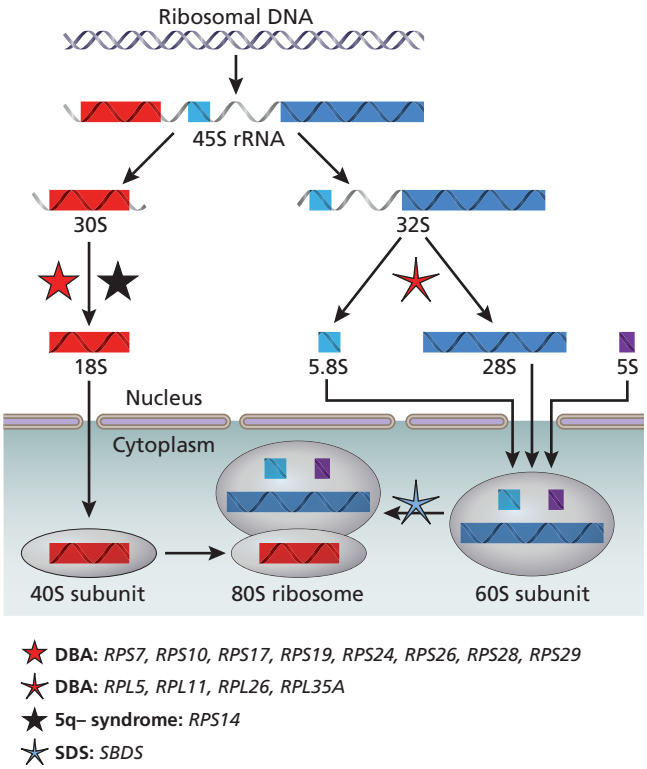

Figure 15-9 Ribosome biogenesis. The schematic shows the scheme of rRNA processing in human cells and the points at which this possibly is disrupted in the different BM failure syndromes. The ribosomal RNAs (rRNAs) are transcribed by RNA polymerase I as a single precursor transcript (45S rRNA). The 45S rRNA is then processed to 18S, 5.8S, and 28S rRNAs. The 18S is a component of the 40S ribosomal subunit. The 5.8S and 28S together with 5S (synthesized independently) are components of the 60S ribosomal subunit. The 40S and 60S subunits are assembled to form the 80S ribosomes. The processing steps affected in Shwachman-Diamond syndrome (most often biallelic mutations in *SBDS*), Diamond-Blackfan anemia (most often due to heterozygous mutations in *RPS19, RPL5, RPS26, RPL11, RPL35A,* and *RPS24*) and 5q− syndrome (haploinsufficiency of *RPS14*) are indicated by the differently colored stars.

SBDS mutations in several young adults (age <40 years) who were not previously diagnosed with SDS, and SDS may be unrecognized in young adults presenting with a myeloid malignancy. MDS/AML develops in SDS patients at an estimated median age of 18 (1-47) years and has poor prognosis. Isochromosome 7q and del(20q) are frequent cytogenetic abnormalities in SDS but do not imply a poor prognosis independent of MDS/AML. Somatic *TP53* mutations are found in SDS-related MDS/AML, and acquisition of biallelic *TP53* is associated with leukemic progression. Somatic *EIF6* inactivation clones that enhance fitness of SDS-deficient cells can be detected in SDS patients who do not develop MDS/AML.

Treatment

SDS-related malabsorption responds to treatment with oral pancreatic enzymes. G-CSF produces an improvement in the neutrophil count, with responses typically observed with lower doses of G-CSF than those required for patients with severe congenital neutropenia.

Cytoreductive chemotherapy for MDS/AML pre-HSCT fails to prevent relapse and carries unacceptably high toxicity in SDS. A recent study from the Northern American SDS registry evaluated outcomes in SDS patients with MDS/AML, most of whom underwent HSCT. The overall survival at 3 years was only 11% for leukemia and 51% for MDS.

KEY POINTS

- SDS is characterized by BM failure (most often neutropenia) and exocrine pancreatic insufficiency.
- SDS is a ribosomopathy, with biallelic mutations in the *SBDS* gene.
- Patients with SDS have a high lifetime risk of developing MDS/AML.

Diamond-Blackfan anemia

CLINICAL CASE

A 6-month-old female infant was evaluated for failure to thrive and pallor. A complete blood count demonstrated isolated macrocytic anemia and reticulocytopenia. BM examination revealed mild hypocellularity with an M:E ratio of >20:1 and no dysplastic features. There was no increase in chromosomal breakage with DEB. The patient was found to have a mutation in the ribosomal protein gene *RSP19*. The same mutation was identified in patient's mother, who has an abnormal thumb and previous history of anemia as a child.

Definition and clinical features

DBA is a hereditary hypoproliferative, macrocytic anemia. DBA classically presents in infants, with most patients diagnosed by 2 years of age. However, an increasing number older children or adults diagnosed with DBA have been noted. BM examination typically reveals a profound paucity or maturation arrest of erythroid precursors in a normo- or hypocellular BM. Differential diagnosis includes transient erythroblastopenia of childhood, parvovirus B19 infection, and other IBMFS.

Inheritance is autosomal dominant, with variable penetrance, but many patients present without a family history and thus presumed or documented sporadic mutations.

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At least 50% of patients have a congenital anomaly, which may involve the thumb or radius, head and face (eg, cleft palate), genitourinary tract, or heart. In addition, many patients have constitutional short stature. However, these anomalies may be subtle, and patients most often present to medical attention for anemia.

Red blood cell adenosine deaminase (eADA) levels and fetal hemoglobin are elevated in most patients and can assist in diagnosis. Patients with DBA have a 5-fold increased risk of cancer, most markedly colon cancer, osteogenic sarcoma, and AML. The North American DBA registry reported an overall cumulative cancer incidence of ~14% by the age of 45 years.

Pathophysiology

Heterozygous germline mutations in the *RPS19* gene, which encodes a ribosomal protein (RP), are found in approximately 25% of patients, while more than 20 RP genes were found to be affected in additional ~50% of patients, leaving 25% without a known genetic diagnosis. Rare patients with DBA phenotypes have been found to have *GATA1* or *ADA2* loss-of-function or *TP53* gain-of-function mutations. Globin-heme disbalance, TP53 activation, and reduced translation are thought to play a role in pathophysiology. While the ribosomal defect primarily causes erythropoietic failure, it can also affect other lineages. Over time, some patients develop hypocellular marrows and/or low platelet and white blood cell counts.

Treatment

In the first year of life, patients are maintained on chronic red blood cell transfusions, with a pretransfusion Hb goal of 9-10g/dL. Approximately one-third of patients show long-term responses to corticosteroid treatment, generally initiated in patients older than 1 year of age due to negative impact on growth and vaccine responses. Patients whose anemia does not respond to steroids or who require steroid doses higher than of 0.3-0.5 mg/kg/d, likely associated with unacceptable short and long-term toxicity, are maintained on chronic RBC support coupled with early and aggressive chelation therapy. The anemia may spontaneously remit later in childhood, but up to 40% of patients remain dependent on long-term RBC transfusions. It is critical that all patients on chronic RBC transfusions are monitored regularly for liver and heart hemosiderosis by MRI, which should guide the intensity of chelation therapy.

Currently, the only curative treatment for DBA is allogeneic HSCT. Recent data suggest excellent overall survival (>90%) for both HLA-matched family and matched unrelated donor transplants.

KEY POINTS

- DBA typically presents in infancy with macrocytic anemia, reticulocytopenia, and marked loss of marrow erythroid precursors.
- Over two-thirds of DBA patients carry mutations in ribosomal protein genes.
- Treatment options for DBA include corticosteroids, RBC transfusion support with iron chelation, and allogeneic HSCT.

Congenital dyserythropoietic anemias

Definition and clinical features

The congenital dyserythropoietic anemias (CDAs) are characterized by anemia with ineffective erythropoiesis, anisopoikilocytosis, multinucleated erythroid precursors in the marrow, and iron overload even in the absence of RBC transfusions, due to increased iron absorption. The 3 classical types (CDA I-III) were historically defined by specific marrow morphologic features; however, genetic classification is proceeding with identification of causative mutations. CDA II can be confused with some inherited hemolytic anemias, especially hereditary spherocytosis, which with it shares clinical findings and an abnormal osmotic fragility test. Other differential diagnoses include hemoglobinopathies, sideroblastic anemias, Pearson syndrome, and MDS.

CDA II, the most common CDA subtype, presents most often in early childhood with anemia of variable severity due to both ineffective erythropoiesis and hemolysis, although up to 40% of cases are diagnosed in young adults. Transfusion dependence is uncommon. Jaundice, hepatosplenomegaly, iron overload, and gallstones are frequent. The reticulocyte count is low, and the BM typically shows multinucleated erythroid precursors, karyorrhexis, and pseudo-Gaucher cells. The RBC membrane in patients with this disorder demonstrates abnormal glycosylation.

CDA I, the next most common form of CDA, usually presents in childhood or adolescence with moderate to severe hemolytic anemia, jaundice, hepatosplenomegaly, normal or elevated reticulocyte count, macrocytosis, and iron overload. Some patients have skeletal anomalies of the distal limbs. BM examination shows erythroid hyperplasia, binucleated erythroid precursors, and a distinctive pattern of internuclear chromatin bridging.

CDA III is a very rare subtype characterized by mild hemolytic anemia with retinal abnormalities and predisposition to monoclonal gammopathy. BM shows multinucleated erythroblasts with many nuclei (gigantoblasts).

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Pathophysiology

Among CDA I patients, the majority (~90%) have biallelic mutations in *CDAN1*, coding for a histone chaperone interacting protein. CDA II is caused by biallelic mutations in *SEC23B*, encoding a protein involved in trafficking of proteins from the endoplasmic reticulum to the apparatus. The autosomal dominant CDA III is due to heterozygous mutations in *KIF23*, encoding mitotic kinesin (MKLP1) that is essential for cytokinesis. Other rare CDA variants are caused by mutations in the erythroid transcription factor genes *KLF1* (autosomal dominant) and *GATA1* (X chromosome).

Treatment

The management of CDA depends on the severity of disease and may include RBC transfusions, iron chelation therapy, or even phlebotomy. Most patients with CDA I respond to interferon-α treatment, which leads to increased hemoglobin levels and decreased iron overload. Splenectomy may reduce transfusion requirements in CDA II. Successful allogenic HSCT has been reported in multiple CDA patients.

KEY POINTS

- The CDAs are characterized by ineffective erythroid production, hemolysis, iron overload.
- Characteristic types of marrow erythroblast morphologic abnormalities including internuclear chromatin bridging (Type 1) or multinucleated erythroblasts (Type 2).

Inherited thrombocytopenias

Thrombocytopenia with absent radii

Thrombocytopenia with absent radii (TAR) is an autosomal recessive disorder characterized by hypomegakaryocytic thrombocytopenia and bilateral radial aplasia. The presence of normal thumbs distinguishes TAR from other IBMFS such as FA. Babies with TAR often have hemorrhagic manifestations at birth (when the diagnosis usually is made), owing to the characteristic physical appearance combined with thrombocytopenia. Additional skeletal (absent ulnae, absent humeri, clinodactyly) and other somatic (microcephaly, hypertelorism, strabismus, heart defects) abnormalities may be seen in some patients.

The platelet count is usually $<50 \times 10^9$/L. The leukocyte count can be normal or raised, sometimes up to 100×10^9/L (leukemoid reaction). BM cellularity is normal, with normal or increased erythroid and myeloid lineages but absent or markedly decreased megakaryocytes. Most patients suffer bleeding events in infancy, requiring prophylactic and therapeutic platelet transfusions, but these events decrease after age 1, conferring a good prognosis in those surviving infancy. There have been no reports of progression to AA but several reports of leukemia, including 2 adults with AML. Whether TAR is associated with an increased risk of hematologic malignancy remains unknown.

TAR is caused by inheritance of both a 200-kb microdeletion including the *RBM8A* gene and low frequency noncoding polymorphisms affecting the other allele. *RBM8A* encodes a protein important for RNA metabolism. Thrombopoietin (TPO) levels are usually elevated in TAR, and thrombopoietin receptor (MPL) expression on the surface of TAR platelets is normal. Therefore, thrombocytopenia does not appear to be caused by a defect in thrombopoietin production. There is some evidence that the phenotype may result from abnormal signal transduction downsteam of TPO binding to the MPL thrombopoietin receptor.

Congenital amegakaryocytic thrombocytopenia

Congenital amegakaryocytic thrombocytopenia is a rare autosomal recessive disorder characterized by absent or greatly diminished megakaryocytes. Patients typically present shortly after birth with symptomatic thrombocytopenia and progress to hypocellular BMF resembling AA, in some cases after a period of improved platelet counts. CAMT is not associated with specific congenital anomalies. There are also case reports of patients with CAMT developing MDS and leukemia.

Most cases of CAMT are caused by biallelic loss-of-function mutations in the *MPL* gene which encodes the TPO receptor. TPO levels are typically high in this form of CAMT. More recently, cases linked to loss-of-function mutations in the TPO gene itself have been reported. Development of AA in patients with CAMT is consistent with evidence suggesting that TPO signaling plays an important role in the maintenance and expansion of HSPCs.

Treatment consists largely of supportive care with platelet transfusions. Fibrinolytic agents may be helpful to treat bleeding. Given that MPL-mutated CAMT HSPCs cannot respond to TPO, TPO agonists such as eltrombopag or romiplostim are not effective in these patients, and such patients with progression to AA or severe thrombocytopenia can be cured by HSCT. Those with TPO mutations will not respond to HSCT but can be treated with eltrombopag or romiplostim.

MECOM-associated syndrome

MECOM-associated syndrome (also termed radioulnar synostosis with amegakaryocytic thrombocytopenia

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[RUSAT]) is characterized by thrombocytopenia progressing to hypocellular BMF and pancytopenia. While heterozygous mutations in the *HOXA11* gene were initially reported in 2 families, mono- and biallelic MECOM gene mutations appear to account for the majority of RUSAT syndrome patients, with a clinical spectrum ranging from isolated radioulnar synostosis with mild thrombocytopenia to severe hypocellular BMF with pancytopenia but without skeletal anomalies. Some patients also have cardiac and renal malformations, B-cell deficiency, and hearing loss. Allogeneic HSCT has been successfully performed in several patients with severe pancytopenia.

KEY POINTS

- TAR is characterized by bilateral radial aplasia caused and isolated thrombocytopenia, with improvement after infancy.
- CAMT is caused by mutations impacting the thrombopoietin axis, either biallelic mutations in the *MPL* gene encoding the TPO receptor or in the *TPO* gene itself, and progresses to pancytopenia.

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